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## ORIGINAL ARTICLES

# THE ROLE OF HUMAN FACTORS IN ACCIDENTAL TRAUMA*

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It is a great honor to be asked to give the second James Stevens Simmons Memorial Lecture. As a friend and colleague, General Simmons was a constant source of inspiration. He created a setting for me and others to develop an extensive experimental program in the field of accidental trauma which is the subject of this lecture tonight. With his extraordinary foresight, he recognized that research in this area should be encouraged and given academic stature in Schools of Public Health. Without his support and leadership, the program at Harvard, and the work of the Commission on Accidental Trauma of the AFEB would not have become a reality[27].

The underlying premise which I propose to develop tonight is as follows: 1) accidental trauma is now a major problem in the field of preventive medicine and public health, 2) human factors play a predominant role in accident causation, and 3) medical officers have an important responsibility in the control and prevention of accidents.

General Simmons clearly stated this thesis in writing the Foreword to my book on occupational health and safety in aviation. I quote: "With the extensive mechanization of our environment, incredible vehicular speeds, and diverse industrial procedures, new threats have appeared to the safety and well-being of many individuals and communities. Therefore, as much attention must now be directed toward the prevention of injuries as is already being given to the control of infectious diseases. Our concepts of preventive medicine must be extended to include health and safety in transit in all forms of transportation and in industry. In this broadened sense, the field of public health can remain one of the major avenues through which our working and fighting manpower can be conserved and strengthened"[9].

A. FREQUENCY OF ACCIDENTS IN CIVILIAN AND MILITARY POPULATIONS. One of the major causes of death and injury in both civilian and military populations relates to accidental trauma. It is not generally recognized that today the loss of life and incapacity resulting from accidents are greater than from any known disease entity. In the United States during 1956, 95,000

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persons were killed in accidents, about 350,000 were permanently disabled, and 9½ million sustained injuries serious enough to keep them from work for one day or longer. These accidents occurred primarily on the highway, in the home, and at work in industrial and agricultural occupations. A million persons have been killed on the highway since the introduction of the automobile, and the direct monetary costs of traffic accidents alone now approach 2% of the national income annually (National Safety Council[22]).

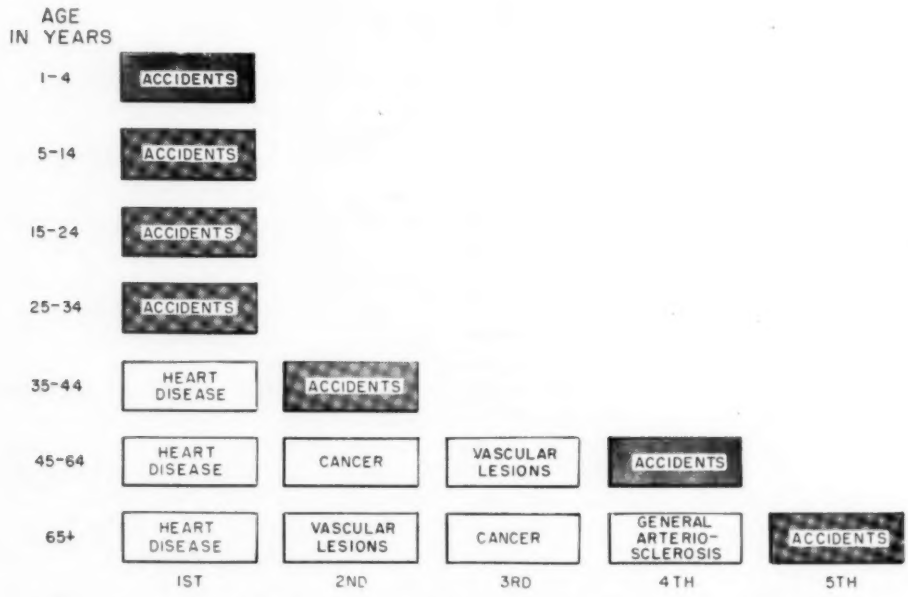


Fig. 1.—The rank of accidents among the leading causes of death, in relation to age. (Data from Vital Statistics: Mortality Data[28].)

Of special importance is the fact that accidents are the leading cause of death in the younger age groups, ranking first for persons between 1 and 34 and second for those between 35 and 44 years. This is illustrated in Fig. 1 (U.S. Department of Health, Education and Welfare[28]). The fact that the victims of accidents are in the younger age groups, in contrast to those whose deaths are attributable to certain degenerative diseases, implies an enormous cost to the productive resources of the country. Measurement of the fact that a death has occurred is less meaningful than the measurement of how much "lifetime" has been lost prematurely.

In the Armed Services, accidental trauma is now a problem of major proportions. During World War II the U.S. Army reported more deaths due to accidents than to disease, for the first time in its history. Every fifth death was related to nonbattle trauma while only every eighteenth was related to disease. For the period 1942–1945, there were 60,054 deaths which were due to nonbattle casualties or a death rate of 3.06 per 1,000 each year (McFarland[19]). For the same period there were15,125 deaths due to disease,

or a death rate of 0.62 per 1,000 each year. In 1953 motor vehicle accidents caused 995 deaths among Army personnel, and were responsible for 19% of the hospital admissions for nonbattle injury. The importance of injury from this latter type of accident in the three branches of the Armed Forces can be judged from Table 1[27]. The trends in the years since have remained essentially the same.

Thus it may be concluded that accidental trauma in both civilian and military populations has attained the epidemic proportions of a noncontagious mass disease. Although some progress in accident control and prevention has been made as a result of research, it is obvious that additional intensive efforts are necessary. Our attitude toward the existence of this epidemic of accidents should be one of

TABLE 1.—MOTOR VEHICLE ACCIDENTS IN THE ARMED FORCES SERVICES—1953

| | *Air Force* | *Navy and Marine Corps* | *Army* |
|---|---|---|---|
| 1. Number injured | 6,726 | 8,488 | 14,190 |
| 2. Fatalities | 740 | 630 | 995 |
| 3. Man-days lost | 162,000 | 336,000 | 810,000 |
| 4. Average days on sick list | — | 43 | 46 |
| 5. Percentage of all accidental injuries | — | 26 | 19 |
| 6. Proportion of injuries off duty | 83% | 88% | 34% |

In the Navy and Marine Corps accidents rank first as the leading cause of man-days lost, a figure approximately three times as great as the next most common cause, namely, upper respiratory infections. Noneffectiveness because of motor vehicle accidents alone in 1953, that is, 336,000 sick days, represents the loss of a full combat battalion of marines or the Navy personnel required to operate three large destroyers. Eighty-eight per cent of those killed or injured were on leave or liberty and over half were injured over the week end.

A similar problem exists in the Air Force, where accidents also outweigh disease as a cause of death and noneffectiveness. Motor vehicle accidents are again the main factor, accounting for 740 deaths and 6,726 injuries in 1953. Each year about 2200 servicemen are killed in off-duty automobile accidents[27].

resentment, as stated by Dr. Alan Gregg in relation to the prevention of disease: "Why do these things keep occurring? Why do they have to continue? Why do they have to be, in the light of what we privately know?"[7]

**Preventive Medicine and the Epidemiological Approach to Accidental Trauma.** A new and comprehensive approach to the control of accidents is needed in which the relationships between the multiple factors in accident causation can be studied and classified. The epidemiological approach developed for the study and control of infectious disease is equally applicable to accidents, and can fulfill such a need. Thus it is proposed that existing concepts of public health be extended to include all elements affecting the well-being of persons in their movement from place to place and while at work. If the end results, rather than the causal mechanisms are made the

basis of definition, then what difference does it make whether large numbers of people are killed or crippled by disease or by injury? Our responsibilities in instituting preventive measures are the same (McFarland[11]).

A. THE ROLE OF PREVENTIVE MEDICINE IN ACCIDENT PREVENTION. It seems only logical, therefore, that public health should assume responsibility for the control of the agents in this threat as it did earlier of those in the quarantinable diseases. In general, accidents follow basic biological laws comparable to those influencing the processes of disease. Accident distributions show variations according to season, age, sex, and other parameters as well (Gordon[6]).

Because of the important role played by human variables, the control of accidents falls within the province of preventive medicine and public health as do the fields of industrial hygiene and sanitary engineering. In most instances, there is multiple causation in accidents and attempts at control should involve consideration of the interaction of host, agent, and environment; that is, the worker, the equipment, and the surroundings or working area. Although the host is of primary medical concern, the agent and the environment must also be considered in effective preventive measures. This applies equally to military and civilian populations, under all conditions, including combat.

The first step in the application of the epidemiological approach should be to set forth the basic physical, physiological, and psychological characteristics of the host. When such facts are associated with the agent under given environmental conditions, information can be obtained which will aid in understanding and preventing accidents. Factual information of this sort can be discovered only by carefully controlled experimental studies, epidemiological surveys, and statistical analyses. A dynamic and continuous safety program is needed. This can produce positive results only by the constant application of the fundamental principles resulting from such studies.

B. ROLE OF THE MEDICAL OFFICER IN ACCIDENT PREVENTION. The medical officer has a direct responsibility in the prevention of accidents, not only because of his broad training in the biological sciences and the important role played by human variables in accidents, but also because he is in an unusual position to teach while treating injuries. One of the basic laws in psychology is that memory operates most effectively when reinforced by emotion. Thus the physician should take the initiative in identifying the causes of accidents leading to their control and indoctrinate patients with the principles of accident prevention while they are being treated.

An example is taken from many serious cases of burns that occurred in an English city in a period of 2 years. Seventy per cent of 1,000 severe burns occurred in children, with girls outnumbering boys 3 to 1. Fifty-three per cent of the girls were injured when their night clothing was set afire by contact with unguarded electric heaters. Why did so many instances occur before such appliances were outlawed by medical authorities, as would have been the case in a question of public sanitation (Colebrook and Colebrook[1])?

Many illustrations can be given of different types of equipment in this country which cause numerous injuries because medical officers fail to consider all the factors of the host in relation to the agent and the environment, and to base prompt corrective and educational measures on such facts. For ex-

ample, accidental poisonings among children are to a large extent a function of the hand-to-mouth period in the child's development. Should not physicians make use of such knowledge in educating parents concerning the special hazards for children of this age if they have access to toxic substances (McFarland[12])?

The next important advances in safety, both in industry and in the services, are most likely to result from more effective collaboration between the engineering and biological sciences. The industrial or military physician can play an important role in reorienting the approach to accident prevention to include the point of view of preventive medicine. This has already been accomplished in some situations.

An example is given below to show how a simple application of this approach has been carried out successfully in the U.S. Army. At one establishment where the accident rate was high, the Safety Director had a card file of the highway accidents of the base personnel, extending over several years. The Medical Officer assisted the Safety Director in analyzing the accident data in an epidemiological manner, that is, in terms not only of location, but also of time of day, rank, and various factors relating to the type of accident. It became apparent that certain features of one highway were especially dangerous, and 90% of the accidents which occurred there took place during a particular 2-hour period in the day. On the basis of the information from this analysis, the Safety Department was able to concentrate patrol activities at the appropriate places and times and to indoctrinate the personnel regarding the characteristic errors in driving which caused most of the accidents. When these procedures were put in effect, there was a substantial reduction in accidents.

The team approach is not new in medicine, and has been essential to many important advances. For example, in the epidemiological study of malaria, collaboration between the entomologist, the sanitary engineer, and other specialists was necessary to secure the basic data and bring about control. The prevention of industrial accidents can similarly be furthered through the aid of the physiologist, the psychologist, the anthropologist, and the safety engineer also cooperating with the physician to try to bring about better control (McFarland[10]).

C. MAJOR AREAS OF RESEARCH. In general, the research program sponsored by the Commission on Accidental Trauma of the AFEB is concentrated on four basic approaches within the epidemiological framework outlined above. 1) *First of all we are trying to identify personality traits and behavior patterns which may lead to repeated errors.* 2) *We are trying to uncover and correct defects in the design of equipment which may lead to, or contribute to, accidents.* This phase of work falls within the realm of human engineering. 3) A third area is concerned with *crash-injury studies of vehicular accidents.* We are trying to identify, and thus eliminate those design features which cause injury or death, in the event of a crash. 4) A final approach is concerned with the *mathematical study of the interrelationships of the various causes* which contribute to accidents[27].

**The Control of Industrial Accidents.** In the United States today there are approximately 65,000,000 people who are engaged in some gainful occupation. It is well known that the military services are the largest employers of civilians, not only in the field of manufacturing, but also in maintenance and

repairs. Improvements have been made in the prevention of injuries while at work, through the traditional safety engineering approaches. Further reductions in accidents can be made only by the application of newer principles from the behavioral and medical sciences.

A. STAGES IN THE DEVELOPMENT OF THE SAFETY MOVEMENT. *The various phases of the industrial safety movement have tended to reflect what seemed to be the major deficiencies at the time.* One of the first stages was characterized by emphasis on *mechanical guarding* and on the educational approach; in the latter, *visual education,* posters, demonstrations, speakers, committees, and safety contests relating to accident prevention are used to create and maintain interest. With increasing experience, it became apparent that more could be accomplished in the control of hazards by stressing the application of basic *safety-engineering principles to the design of machinery, plant layout, and working methods.* Gradually, more emphasis was placed on the role of *supervisory personnel,* and the foreman was charged with the responsibility for accidents. The role of *personal errors and accident proneness* has been emphasized by stressing the proper placement of the employees, based on job analyses and the functional capacity of the worker ([9] esp. Chap. 11).

It is now generally recognized that accidents result from a combination of causes, rarely from just one cause. Attempts at control or prevention must, therefore, involve consideration of the host, that is, the human operator, the agent, that is, the equipment, and the environment, that is, the general work setting with all its various interrelationships. Human factors appear to be of greatest importance and the following epidemiological methods are relevant:

1) Determination of existing status and behavior of the disorder in the community or universe being investigated.

2) Determination of causes related to the status of the specific disorder.

3) Development of specific measures for adequate control.

4) Evaluation of results that come from recommended procedures.

Finally, the prevention of accidents is a fundamental responsibility of management to be dealt with in terms of basic design and operations and at executive levels. Commanding officers in the military services can play a similar role in bringing about a reduction of accidents.

B. AN EPIDEMIOLOGICAL DESCRIPTION OF SELECTED INDUSTRIAL ACCIDENTS. One of the greatest difficulties in the study of accidents is to obtain an adequate description of what occurred and under what conditions. An illustration of what can be done by the accurate recording of such information is afforded by a study made by an industrial physician in Ohio. *The accident distributions showed regular variations according to age, sex, time of day, season of the year, and other parameters. It was found that 50% of the injuries occurred to people under the age of 25. The rate for the 20 to 24 year group was over twice that of the 40 to 44 year group. A diurnal cycle was observed which had a low at 5 A.M. and a high at 5 P.M. The various types of accidents showed a high degree of regularity; 80% occurred from either falls, aggressive behavior, handling objects, stumbling over objects, vehicular equipment, or involved foreign bodies* (Schulzinger[23]).

In a recent survey of several military establishments in the Boston area, it has been observed that a further reduction in accidents could result if more attention were paid to time of

day, month, and prevailing weather when accidents occurred. This could also be enhanced by making available basic population data and accident rates by type of employment and age groups. The greatest need appeared to be more extensive use of periodic physical examinations in combination with the work of job analysts so as to match the abilities and physical capacities of workers to the demands of jobs (Hanman[8], and U.S. Armed Forces Epidemiological Board[27]).

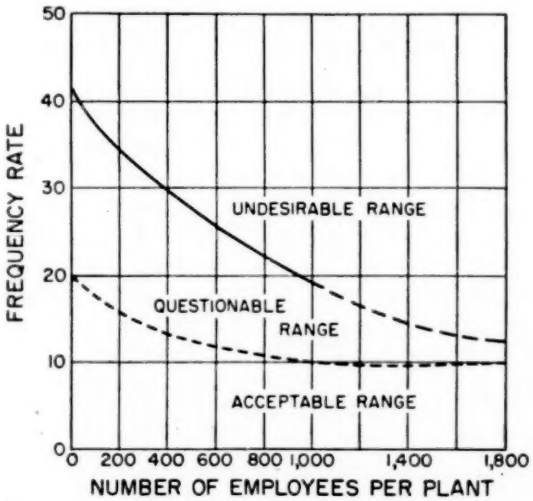


Fig. 2.—The relation of plant size to frequency of industrial accidents. The curves are based on a survey of accidents by a large insurance company and indicate the tendency toward lower accident frequency rates in larger companies having better control measures (*cf.* McFarland[9]).

There is a tendency for larger companies to have lower frequency rates than the smaller ones, as indicated in Fig. 2, but many of the latter have excellent records. In small plants the owner or manager is apt to be in close contact with operations, but in medium size ones the owner is apt to lose personal contact. In large plants a company can support a safety engineer and provide in-plant medical facilities. The size of a company, however, is of less importance than the degree of control exerted by management to prevent accidents.

In the field of air transportation, industrial accidents in ground operations present a serious problem. An analysis of accident injury rates by class of personnel in the civil airlines has indicated that consistently, year after year, both frequency and severity rates have been excessive among the workers in line maintenance and base repair shops. On the other hand, general office, traffic, station, and operating personnel have presented no particular problem in respect to either the frequency or severity rate. Table 2 presents a breakdown of accident rates among airline ground personnel for the 5-year period 1950 to 1954. The same trends have continued since (McFarland[9]).

One of the most important contrib-

uting factors to the poor record in the line maintenance and base repair shops is the wide diversity of occupational hazards that are present within the limited working areas of hangars and ramps. In these large overhaul bases men from 50 or 60 different vocational groups are required to work at high speed, often close together in small quarters. Some of the workers are exposed to bad weather and working surfaces covered with ice and snow. Another factor is the nonrepetitive nature of many of the duties, and airline experience parallels that in other industries where nonrepetitive workers also tend to have high injury rates. In the Air Force, as well as in civilian aviation, the high injury rate for industrial accidents constitutes a major problem.

When the medical and first aid records of a number of the larger companies were studied, one of the most striking features was the *consistency* with which particular types of injuries were repeated year after year. This is illustrated in Table 3 (McFarland[9]).

TABLE 2.—ACCIDENT FREQUENCY RATES IN AVIATION GROUND EMPLOYEES

| *Year* | *Number of Companies* | *Group I General Office and Traffic Personnel* | *Group II Station and Operating Personnel* | *Group III Line Maintenance and Base Repair Workers* |
|---|---|---|---|---|
| 1950 | 11 | 2.8 | 11.6 | 33.5 |
| 1951 | 10 | 2.8 | 16.0 | 29.3 |
| 1952 | 14 | 1.7 | 16.3 | 26.1 |
| 1953 | 16 | 1.6 | 16.3 | 17.1 |
| 1954 | 18 | 1.4 | 20.1 | 21.0 |

TABLE 3.—NUMBER OF FIRST AID TREATMENTS AMONG 1,500 EMPLOYEES IN A LARGE MAINTENANCE UNIT, DURING A 2-YEAR PERIOD

| | *First Year* | | *Second Year* | |
|---|---|---|---|---|
| *Type of Injury* | *January–June* | *July–December* | *January–June* | *July–December* |
| Total injuries | 1,873 | 1,751 | 1,865 | 2,170 |
| Selected Injuries: | | | | |
| *Laceration or Abrasion:* | | | | |
| Head | 82 | 79 | 104 | 118 |
| Hand or finger | 806 | 735 | 766 | 857 |
| *Eye Injuries:* | | | | |
| Foreign bodies, solid | 210 | 215 | 273 | 310 |
| *Puncture:* | | | | |
| Hand or finger | 256 | 161 | 168 | 178 |
| *Sprains & Strains* | 48 | 32 | 62 | 68 |

It was also of interest to note changes which could be related to specific preventive practices. Such data have considerable significance for the proper training and supervision of employees, as well as for the design of protective devices.

As an additional precautionary

measure in the control of accidents, an illustration can be given from one of my own studies on the application of statistical quality control methods to first aid injuries. In Fig. 3 the normal or expected rates based on past experience are indicated by the dashed horizontal lines. Periods in which the number of first aid injuries per 1,000 man-hours go beyond these calculated limits indicate the need for prompt investigation and appropriate action (McFarland[9]).

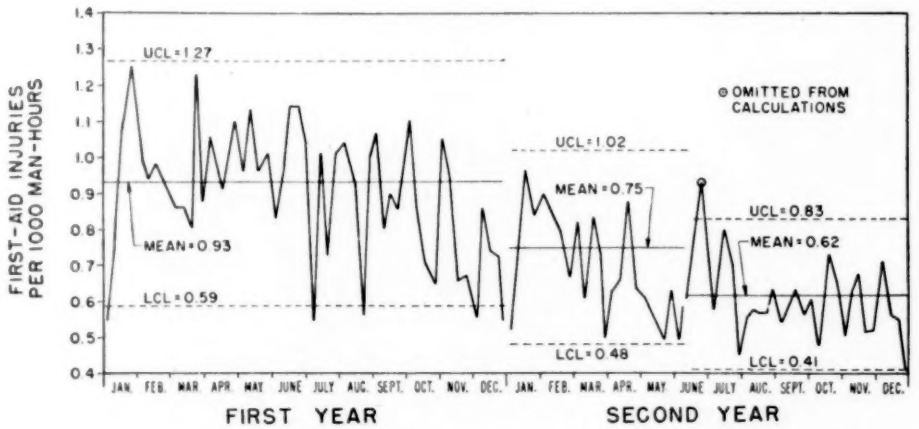


Fig. 3.—The use of statistical quality control for industrial safety. Normal or expected rates based on past experience are indicated by the dashed lines. Periods in which the rates go beyond these calculated limits indicate the need for prompt investigation and appropriate action (From McFarland[9]).

There are a few points to be made briefly in regard to the role of environmental variables in causing accidents. The environmental influences which may affect the efficiency and safety of the operators of various types of equipment are shown schematically in Fig. 4. These are fairly well understood if considered as single variables. For example, if noise levels exceed certain limits, speech communication may be impaired and safety compromised. The difficulty of using a single numerical value, however, may be illustrated by the effects of carbon monoxide on pilots. The generally accepted standard of safety is 0.005% carbon monoxide in circulating air. This figure may be satisfactory for a person sitting quietly at sea level, but it should be reduced if the amount of exercise, amount of ventilation, or the length of time increases. If the pilot is a chronic cigarette smoker, there may already be 5 to 10% carbon monoxide in his blood. In flight, his physiological altitude may be materially increased by the combined effects of the lowered amount of oxygen available at high altitude, the ambient carbon monoxide in the aircraft, and the carbon monoxide from smoking. The same complexity characterizes almost every other environmental variable. Thus a series of variables has to be considered, and their effect upon human performance and safety can best be understood, not in terms of linear scales, but through developing nomograms where the influences of several variables at the same time can be evaluated (McFarland[13]).

**Control of Transportation Acci-**

**dents.** The extensive use of some kind of motor vehicle is now generally accepted as the primary means of transportation. The marked increase in the number of automobiles, trucks and buses in recent years constitutes the most outstanding development in our economy. One of the most important implications of the above change in the national scene relates to safety in transit. As miles traveled, passengers carried, and tons conveyed have increased, traffic has become more dense, speed levels have risen and there has been, as a direct result, an increase in deaths, injuries, and monetary costs. Thus, the integration of motor vehicles into our way of life has become very costly, and highway safety has become a matter of pressing national concern.

Many contend that the great volume of traffic on our highways and the increasing speed, power, and complexity of modern equipment can only be expected to result in many accidents. Many improvements have been incorporated in all types of vehicular equipment, and this is borne out by the fact that the fatal accident rate per 100 million vehicle miles has de-

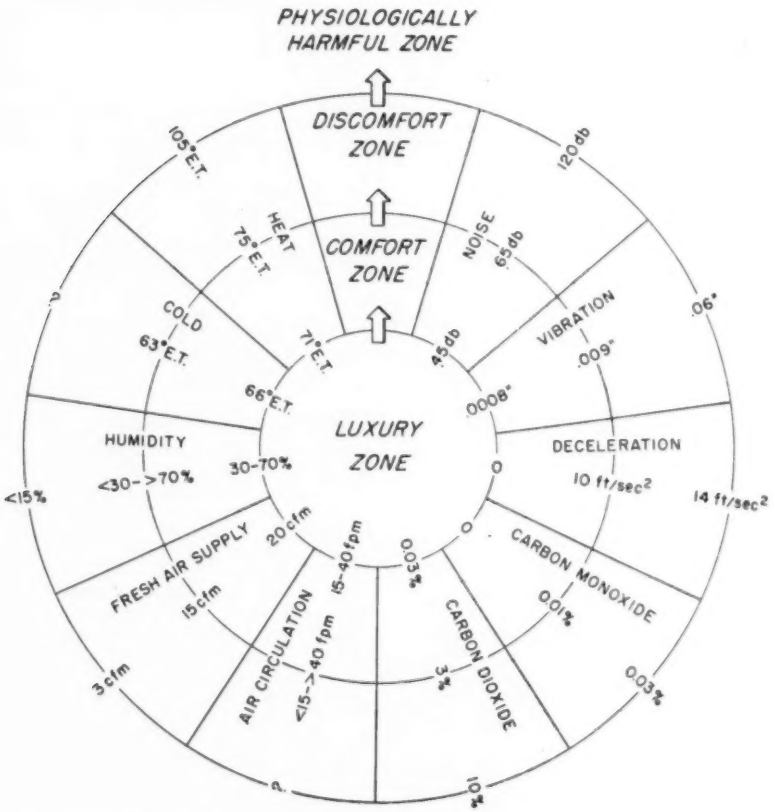


Fig. 4.—The physical variables of the environment influencing driver comfort, health, and safety. These values must be considered approximations since each variable is interdependent on one or more additional factors (From McFarland[13]).

creased from 15 to 6.5 in the past 25 years, as shown in Fig. 5. Nevertheless, as may be seen in Fig. 6, the total of traffic deaths each year remains high and there were approximately 38,300 deaths, 110,000 permanent disabilities, and over one million disabling injuries in 1955. There were 40,000 deaths in 1956. It has been estimated that one person in every ten will be killed or injured in a motor vehicle accident within a period of 15 years (McFarland, Moore, and Warren[18]).

Possibly the mood and the tempo which gives rise to these alarming rates are as well described in the words of a poet, T. S. Eliot[4], as by a scientist.

"And now you live dispersed on ribbon roads,
And no man knows or cares who is his neighbour
Unless his neighbour makes too much disturbance,
But all dash to and fro in motor cars,
Familiar with the roads and settled nowhere.
Nor does the family even move about together,
But every son would have his motor cycle,
And daughters ride away on casual pillions."

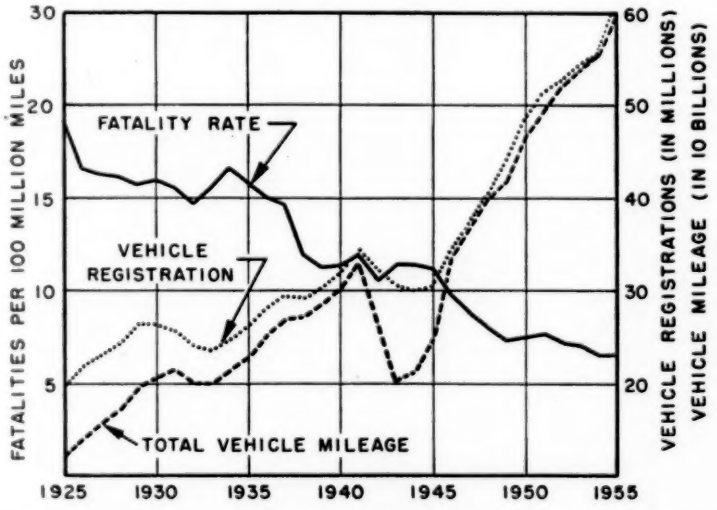


Fig. 5.—Fatality rates in motor vehicle accidents compared with vehicle registrations and total vehicle mileage, 1925–1955 (From McFarland, Moore, and Warren[18]).

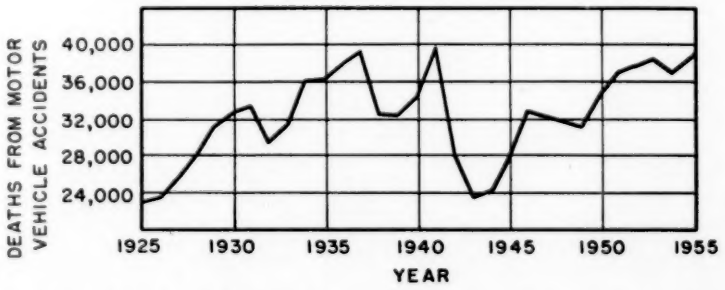


Fig. 6.—Annual totals of deaths resulting from motor vehicle accidents, 1925–1955 (From McFarland, Moore and Warren[18]).

A. HOST FACTORS: THE CHARACTERISTICS OF DRIVERS IN RELATION TO HIGHWAY SAFETY. A wide variety of sensory, psychomotor, psychological, and physical characteristics have been investigated in relation to the accident frequencies or accident rates of drivers and groups of drivers. Although highway accidents are usually attributed to human failure of some kind, close and invariable relationships between particular characteristics of drivers and the frequency of accidents have not been found. Some traits have been of importance in some accidents, but not in others. Thus far no single characteristic of drivers has been isolated which appears to be outstanding in accounting for a large proportion of accidents on the highway.

Those attributes of drivers bearing a gross statistical relationship to accident frequencies include low intelligence, youthfulness, and a personality make-up in which social responsibility is weak or lacking (McFarland, Moore and Warren[18]). The influence of youthfulness is illustrated in Table 4, based on the accidents sustained during the first 9 months of 1955 by drivers licensed in Connecticut[2].

TABLE 4.—ACCIDENTS AMONG SELECTED AGE GROUPS OF DRIVERS LICENSED IN CONNECTICUT, 1955

| | | *Involved in Accidents* | | *Involved, at Fault* | |
|---|---|---|---|---|---|
| *Age Group* | *Licensed* | *Number* | *Per Cent* | *Number* | *Per Cent* |
| 16 | 4,700 | 720 | 15 | 490 | 10 |
| 17 | 12,900 | 880 | 7 | 525 | 4 |
| 18 | 16,200 | 890 | 5.5 | 560 | 3.5 |
| 19 | 18,200 | 840 | 4.7 | 500 | 2.8 |
| 20 | 19,000 | 800 | 4.2 | 470 | 2.5 |
| 35 | 30,000 | 790 | 2.6 | 340 | 1.1 |
| 40 | 28,000 | 725 | 2.6 | 313 | 1.1 |
| 50 | 18,500 | 473 | 2.6 | 214 | 1.1 |
| 60 | 11,400 | 290 | 2.5 | 134 | 1.2 |

1. *Studies of accident repeaters.* One aspect of the host, or driver, that has received a great amount of attention in recent years concerns the concept of accident proneness, or repeaters. This originated in part from the reports of industrial physicians who noticed that a small proportion of workers in their plants seemed to be responsible for a large proportion of the accidents. One medical department, for example, reported that 80% of the visits to the clinic were made by 30% of the plant population. The observation that a small number of workers or drivers were responsible for most of the accidents led to the assumption that these workers were accident-prone.

Some doubts have been thrown on this assumption by the statisticians. If one applies the Poisson curve to the distribution of accidents among the workers in any large industrial group, a small proportion of the group would be expected to have most of the accidents, purely as a result of chance (Thorndike[25]) (see Table 5).

When there is an excess of workers with repeated accidents over the number to be expected by chance, the problem becomes whether these workers are accident-prone, and how to locate the most susceptible workers to eliminate or retrain them. Studies in this vein have so far been largely negative. For example, in Table 6

TABLE 5.—CHANCE DISTRIBUTION OF 300 ACCIDENTS IN A GROUP OF 500 PERSONS

| *Accident Frequency, per Person* | *Theoretical Number of Cases* |
|---|---|
| 0 | 275 |
| 1 | 165 |
| 2 | 49 |
| 3 | 10 |
| 4 | 1 |

TABLE 6.—CHANCE AND OBTAINED DISTRIBUTION OF 7,288 ACCIDENTS FOR 17,952 PILOTS DURING AN 8-YEAR PERIOD

| | *Number of Pilots Associated with Number of Accidents* | |
|---|---|---|
| *Number of Accidents* | *Chance Distribution* | *Obtained Distribution* |
| 0 | 11,962 | 12,475 |
| 1 | 4,856 | 4,117 |
| 2 | 986 | 1,016 |
| 3 | 133 | 269 |
| 4 | 14 | 53 |
| 5 | 1 | 14 |
| 6 | 0 | 6 |
| 7 | 0 | 2 |

the actual distribution of accidents during an 8-year period in a large group of aircraft pilots is shown, along with the theoretical distribution computed on the basis of chance. There is a slight excess, over chance, of pilots with no accidents and of pilots with multiple accidents. This difference is so slight as to indicate a very negligible, if any, effect of accident-proneness. It may, in fact, be due to nonpersonal factors, such as differences in types of mission, or in types of planes flown by the individual pilots (Webb[29]).

Another approach has been, in particular industrial groups, to correlate the accidents sustained in one period with those sustained in a later period, to see if the same people had high accident frequencies in both. The controlled studies of this sort have also turned out to be generally negative, that is, the same people did not have the accidents in both periods. It seems probable that an individual may have temporary predisposing conditions of a physiological or psychological nature, or be exposed to variables in his environment which may lead to his becoming involved in an accident. It is, therefore, necessary to analyze the total accident situation to locate the "focus of infection."

Without waiting for statistical proof of accident-proneness, an obvious place for the industrial physician to start is with those individuals in any industrial group who have a history of repeated accidents, and who, therefore, may be most susceptible. The clinical approach is one direct way of determining whether these individuals are adapted to their jobs.

2. *Clinical studies of accident repeaters.* A psychiatric view of accident-proneness has originated from the work of Dunbar, who compared fracture patients with other types of patients in a New York hospital. She believed that the fracture patients showed signs of repressed guilt and resentment, and traced their accidents to these unconscious feelings[3]. Thus accidents, in this view, are motivated, and an elaborate set of psychiatric concepts has been developed to explain the repeated accidents of certain people. In considering these studies, it is important to realize that emotional

states are undoubtedly of significance in many accidents, but it would be an unimaginative psychologist or psychiatrist who could not, *after* an accident has occurred, find some indication of the conflicts and repressed feelings consistent with this theory.

It seems obvious that objective methods need to be developed of "predicting," or identifying in advance those likely to have repeated accidents, if the control of accidents is to be achieved through attention to this records, public health and venereal disease rates, credit bureau and social service agency contacts. The basic concept in this work was that the people involved in repeated accidents are those who have evidenced maladjustments in meeting other personal and social demands of life. In this particular study, 66% of the accident-repeaters were known to one or more of these agencies, against only 9% of those who were accident-free (Fig. 7) (Tillmann and Hobbs[26]).

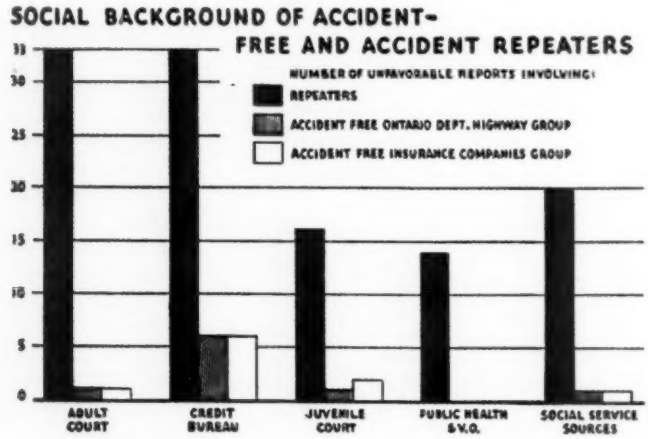


Fig. 7.—The comparison of 96 accident-repeater drivers with two groups of 100 accident-free drivers in terms of a record of contact with selected agencies (From Tillmann and Hobbs[26]).

characteristic of the host. In one provocative study, individuals having repeated accidents were matched with others who were accident-free, and compared in respect to their social adjustments (Wong and Hobbs[30]). Dr. Tillmann has now utilized this method with groups of industrial workers, drivers, and with groups of airmen in the Royal Canadian Air Force. For example, groups of accident-repeater drivers were matched with accident-free groups and compared in terms of their adult court

At the Harvard School of Public Health we have repeated this approach by carefully matching accident-free and accident-repeater truck drivers in all the essential aspects of their work and driving experience. Very rigid criteria were set up, using a large number of cases obtained from the Interstate Commerce Commission. The procedure was found to distinguish clearly between accident-free and accident-repeater drivers. The relative value of selected items in discriminating the good and poor drivers is shown

in Table 7. The Chi square values for the discriminating items were then used as weights for the items in a test. When this test was tried on an unselected sample of drivers, it was possible to identify 85% of the accident-repeaters (McFarland and Moseley[19]).

It may be concluded from these studies that "a man drives as he lives." This recalls to mind the view of the cardiologists, that the way a man lives in regard to diet, exercise, relaxation, and nervous tensions, determines how long he lives. In general, those adults having repeated accidents may be characterized as having a disrespect for organized authority, showing poor social adjustment, and giving evidence of permanent or transitory emotional instability. Just as delinquency may be a manifestation of the above-mentioned traits, so also may repeated accidents reflect the type of adjustment or mode of life.

TABLE 7.—RELATIVE VALUE OF SELECTED ITEMS TO DISCRIMINATE BETWEEN ACCIDENT-FREE AND ACCIDENT-REPEATER DRIVERS

| *Item* | *Chi²* |
|---|---|
| Court record of automotive offenses | 7.48 |
| Minor violation in motor vehicle records | 6.76 |
| Court record of offenses against persons | 6.43 |
| Unfavorable business inspection report | 3.84 |
| Court record of offenses against self | 2.55 |
| Court record of offenses against property | 2.01 |
| Accident in motor vehicle records | .61 |
| Licenses suspension, in motor vehicle records | .60 |
| Serious violation, in motor vehicle records | .03 |

The important role of factors of personality and personal adjustment in causing accidents is being further investigated in an extensive research project at the University of Colorado, sponsored by the Commission on Accidental Trauma of the Armed Forces Epidemiological Board. There workers are attempting to relate the findings on a selected battery of psychological and personality tests, and from intensive psychiatric interviews, to the accident records of a large number of drivers. The results so far indicate that accident repeaters give a highly consistent pattern on one test of personal values (the Allport-Vernon Scale of Values). Drivers having accidents frequently scored consistently low on religious values and high on aesthetic and theoretical values. With properly chosen cut-off scores, this test differentiated accident-repeater drivers from nonaccident drivers with an accuracy of over 70% (AFEB[27]).

One aspect of the above research makes it of special interest to the military services, in that arrangements have been made to secure test and interview data on a large number of high school sophomores, and to follow the driving and accident experience of this group over a 3-year period. Since this age group represents the greatest segment of the military manpower pool, this long range predictive study should yield information of considerable value to the Armed Services.

3. *Temporary states of the host.* A wide variety of temporary states and conditions also influences highway safety through their effect upon the behavior and efficiency of drivers. The influence of such states is usually difficult to determine statistically, although they are believed to be responsible for many accidents.

a. FATIGUE. The effects of fatigue are most pronounced in driver-asleep accidents. In many other situations, it is difficult to determine the loss of efficiency due to fatigue. It has been demonstrated that subjects do less well on a variety of psychological and psychomotor tasks after prolonged driv-

ing. The results have been interpreted to indicate reduced efficiency, and hence increased liability to accidents. Such findings provide some evidence for the regulations governing hours of driving and intervening rest periods which have been adopted by the Interstate Commerce Commission (McFarland, Moore and Warren[18]).

Evaluating the role of fatigue in highway safety, however, is not simply a matter of relating hours of driving to accident frequencies. Actually, in the case of truck drivers, the greatest frequency of accidents (about 60%) is found within the first 3 hours of driving rather than near the end of the day's run. The amount and quality of previous rest, time since last rest, the nature of activities prior to driving, and concurrent emotional stress are some of the numerous complicating factors[19].

A clearer understanding of the effects of fatigue on driving performance can be gained from the concept of skill fatigue. A complex skilled performance such as driving has been shown to deteriorate in characteristic ways under protracted operation, or under other fatigue-producing conditions. One initial effect concerns the timing of reactions. While in later stages gross mistakes may appear, at first it is more likely that the right response is made, but at the wrong time. As fatigue increases, the field to which the operator is responding as a whole loses its integrated quality, and the operator reacts to individual aspects of it. Certain stimuli predominate, while others are ignored and important responses are omitted. Standards of performance deteriorate and the operator thinks he is doing as well as previously while he is actually operating less skillfully, and no longer recognizes or appreciates his errors. There may be loss of insight into the seriousness of the situation.

Under conditions of extreme fatigue, drivers may experience hallucinations of obstacles on the highway. Confidential interviews with 53 commercial drivers revealed that a majority of them had experienced such reactions. A number of accidents have resulted when the drivers maneuvered to avoid hitting various objects or animals perceived but not actually present. These experiences occurred most frequently on long distance runs at night, and when driver activity level was low and he felt a need for sleep (McFarland and Moseley[19]).

TABLE 8.—RELATIVE FREQUENCY OF AUTOMOBILE ACCIDENT CASES FOR DIFFERENT ALCOHOL CONCENTRATIONS

| *% Alcohol in Blood* | *Number of Accident Cases Per 100 Control Cases* |
|---|---|
| none | 9 |
| less than .04 | 45 |
| .04–.07 | 21 |
| .08–.11 | 53 |
| .12–.15 | 146 |
| .15 and over | 577 |

b. ALCOHOL. Alcohol also has a temporary effect on the driver, and is known to be an influence in causing highway accidents. Measuring the extent of the influence of alcohol in accidents presents statistical difficulties, however, because of the necessity of having control data. One study in which controls were observed is summarized in Table 8, which indicates that the likelihood of accident increases even at low levels of alcohol in the blood. Higher levels are characterized by a sharply increasing likelihood of accidents (Thorndike[25]).

Various laboratory investigations have also shown that the effects of alcohol, although subject to wide vari-

ations in individual susceptibility, are always in a deleterious direction on a variety of sensory, psychomotor, and psychological functions. Of particular importance for driving is the effect involving reduced standards of performance and a loss of insight into the quality of performance.

In a recent study of 900 necropsies of drivers who were highway casualties in the State of New York, it was found that over 50% had significant amounts of alcohol in their blood or brains[24].

c. THE INFLUENCE OF DRUGS AND MEDICATIONS. More also needs to be known regarding the principal action or the side effects of commonly used medications and drugs on the safety and efficiency of performance at the wheel. It is not always realized, for instance, that a sedative effect persists up to 24 hours after the ingestion of some preparations ordinarily prescribed for relaxation and sleep. Disturbances of vision and of equilibrium, and episodes of drowsiness have also been reported in some persons after self-medication with over-the-counter preparations to relieve pain or the symptoms of colds. Research at the University of Rochester has suggested that a number of medicinal preparations have effects upon attitudes and behavior which may be of importance in safety as reflected in the driving practices displayed by persons while influenced by such substances[21].

4. *Medical considerations.* There are frequent newspaper accounts of drivers who have experienced serious accidents because of advanced physical disabilities, such as heart failure, diabetes, or epilepsy. For example, the *New York Times* recently reported the case of a man who died of heart disease while driving. His car killed 2 boys standing near their bicycles at the side of the road, and finally stopped in the lobby of a moving picture theater which fortunately was empty at the time.

Limiting the driving of persons with various illnesses or disabilities presents a serious problem. The need for research to evaluate the influence of specific diseases in traffic accidents, and to establish medical criteria and cut-off points regarding fitness to drive was clearly brought out in a recent conference on medical factors in highway safety at New York University-Bellevue Medical Center. For example, there are approximately 150,000 epileptics in New York State, yet only 150 driving licenses carry this notation in regard to the statement of physical condition. What do we really know about the importance of such conditions in highway safety, and how can we get the data to determine the contraindications to driving more accurately?

The trend in the regulations on licensing in the various states is to exclude from driving those individuals with severe sensory and perceptual defects; those with amputations or disturbances of motility which would interfere with the normal operation of controls; those with conditions leading to possible lapses of awareness or periods of unconsciousness; those with drug or alcohol addiction; and those with severe mental defect or disorder. An individual diagnosis is needed in such instances, and arbitrary regulations cannot be satisfactorily set regarding disqualifying conditions[21].

The American public is very reluctant to accept a limitation on personal freedom, especially in regard to the privilege to drive. For example, what about the diabetic driver? Most authorities would agree that a diabetic who requires insulin should not drive a school bus or a public conveyance. However, if the problem of medical fitness to drive is to be satisfactorily

worked out, we must have large scale studies of people with these diseases, to try to let them help decide which of their group should not drive.

A physiological and clinical study of one thousand persons with diabetes, together with statements from them about how they have been influenced in a dangerous way might not only make an important contribution but would be a much more successful approach than setting up arbitrary cut-off points, without an experimental basis. In fact, we are planning such a study at the Harvard School of Public Health, in collaboration with Dr. Howard Root, Director of the Joslin Clinic.

B. HOST-AGENT RELATIONSHIPS, AND THE ROLE OF HUMAN ENGINEERING. A promising approach to the prevention of accidents involves a closer integration of the engineering and biological sciences in the development of equipment. In terms of our epidemiological analogy, the "agent," that is, the equipment, must be considered in its relation to the "host," or operator. Many errors which have been attributed to human failure are actually as much a function of the equipment. It is possible to show that many accidents in the Armed Services, on the highway, and in industry have occurred because equipment was not designed in terms of the human limitations and capabilities (McFarland[14]): Several examples may help to clarify this point of view.

The first illustration is taken from the field of aviation. Confusion has arisen when the controls for operating the flaps and landing gear are located too close together, or reversed from one plane to another. In one 22-month period during World War II, inattentive manipulation or mistaken identity of these controls caused 547 accidents in one of the services. Of these, 273 were in advanced trainers and 184 in fighters, bombers, and transports (McFarland[15]). Another example relates to a serious highway accident which resulted when the driver of a modern automobile, traveling at high speed at night, inadvertently shut off the headlights in the belief that he was pushing the cigar lighter. The knobs for these two were identical in shape and size and were located next to each other on the dashboard.

It was clearly brought out in World War II that machines do not fight alone, and that the effectiveness of any man-machine system depends upon the integration of the operator with his equipment. Ideally an advance analysis of all types of equipment to detect errors in design should be made at the planning stage. The physician, because of his background in the biological sciences is in an excellent position to recognize instances where human requirements have been overlooked in the design of equipment, thereby predisposing the operator to accidents.

The advance analysis of equipment requires an operational analysis of the job, including a survey of the responses to be performed, the layout of the working area, the location of controls and instruments, and the way the operator carries out his functions. A functional concept of accidents is a basic consideration. That is, the errors and accidents which may occur during operation should be anticipated. Human limitations also must be considered. If the duties are too complex, the operator may be forced beyond his limits of attention and ability. Finally, a wide margin of safety should be provided to prevent situations which place the operator near his maximum aptitude or effort, especially as adverse factors such as fatigue or physiological stress are encountered.

If the viewpoint of human engineering, or biotechnology, is carried out in

practice, fewer errors and accidents in the operation of equipment should result. Dials, gauges, and all devices intended to convey information should be considered as extensions of the operator's nervous system and perceptual apparatus. Levers, pedals, and controls should be considered as extensions of his hands and feet, taken as simple tools. Finally, care should also be taken to avoid interference with established habit patterns. Otherwise, it is hardly fair to attribute so many accidents to human failure as is usually the case (Fitts[5]).

operate the hand brake comfortably. In others, there was insufficient clearance between the brake pedal and steering wheel for a taller driver to operate the foot brake except by angling the knee out to the side; this clearance was adequate for only 60% of the drivers. In one of these models, the tallest 15% of drivers would be unable to raise the foot to the brake pedal when the shift lever was in either of the two left positions, since the lever prevented the taller driver from moving his knee to the side of the wheel. Numerous instances were also ob-

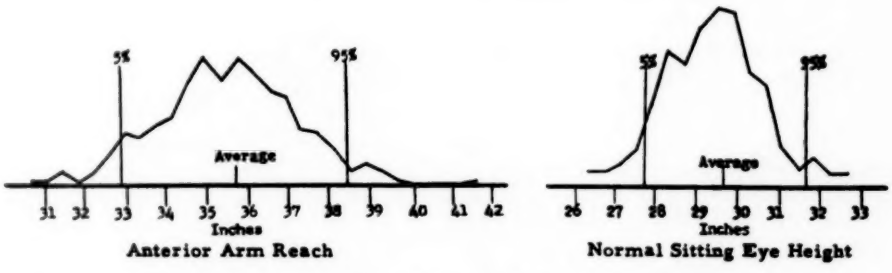


Fig. 8.—The distribution of measurements of arm reach and sitting eye height for professional bus and truck drivers (From McFarland and Moseley[19]).

One of the important considerations relates to the *range of human body size*. If vehicular equipment, for example, is designed for the person of average size, a considerable proportion of drivers who are either larger or smaller than the average may be discommoded in various ways. As a part of a study at Harvard on how well commercial vehicles are suited to their operators, an anthropological team measured approximately 400 truck drivers, in various sections of the country. The distributions for two of the dimensions which are of special importance in driving are shown in Fig. 8.

In several of the truck models studied, only 5% of the driver population could be expected to reach and served where the location of controls or switches made their operation difficult. For example, in some trucks the dimmer button was located directly underneath the clutch and brake pedals, and very close to the steering post (McFarland and Moseley[19]).

While anthropologic data on static human dimensions are of great importance for the design of equipment, consideration must also include the dynamics and biomechanics of men at work. One needs to study how a man is seated at his job, how far he has to reach, what force he can bring to bear on his controls, and to design the work space and controls in the light of the operator's capabilities and limitations. The use of mockups of equipment is an essential step which reveals

many design errors not apparent at the blueprint stage.

In the evaluation of vehicles mentioned above, it was found that *the design of many dials and gauges* could be expected to hinder rapid and accurate reading of the information they convey. The following factors are important in regard to the ease of seeing: a) size and spacing of critical detail, especially in instrument markings and figures; b) contrast between object and immediate background; c) amount of illumination, including the use of color; d) contrast between the objects to be seen and their surrounding. Design criteria for dials, gauges, and pointers, based on human visual capacities, have been determined experimentally (Fitts[5] and McFarland[15]).

In general, it may be said that any control unnecessarily hard to reach and operate, any instrument difficult to read, any seat inducing poor posture or discomfort, or any unnecessary obstruction to vision may contribute directly to an accident because of the effect on the performance of the driver. Man is a poor monitor of equipment, and where safety considerations are involved, anything which might be done to monitor the driver by means of warning devices is highly desirable. In addition, it should be kept in mind that both men and machines are likely to become unstable or break down under overloads. Finally, the cumulative effects of undue burdens imposed by poor design features are sure to induce fatigue, resulting in the overall deterioration of operating efficiency and perhaps leading to an accident.

C. THE HOST-AGENT-ENVIRONMENT RELATIONSHIPS. A consideration of great importance in understanding and preventing accidents relates to the interactions between the host, the agent, and the environment in creating hazardous situations. The influence of certain variables in the environment on the efficiency and safety of industrial workers has been mentioned previously in terms of physiological and psychological limits (see Fig. 4).

The epidemiological approach toward the control of accidents can be studied in fairly quantitative terms. There is only time for an analysis of a few variables to demonstrate the principles involved. The first example will be taken from the field of human vision in reference to the level of illumination in the environment and the high incidence of night accidents on the highway.

TABLE 9.—CHANGE IN ILLUMINATION NECESSARY TO SEE A STANDARD, BRIEFLY-VIEWED, MOVING STIMULUS WITH INCREASING AGE

| | *Relative Illumination Necessary* | |
|---|---|---|
| *Age Group* | *In Presence of Glare Source* | *Without Glare Source* |
| 15–19 | 1.00 | 1.00 |
| 20–24 | 1.15 | 1.10 |
| 25–29 | 1.28 | 1.17 |
| 30–34 | 1.35 | 1.20 |
| 35–39 | 1.54 | 1.27 |
| 40–44 | 1.78 | 1.33 |
| 45–49 | 2.24 | 1.48 |
| 50–54 | 2.83 | 1.94 |
| 55–59 | 3.42 | 2.32 |
| 60–64 | 5.18 | 2.92 |
| 65–69 | 10.25 | 4.47 |
| 70 and up | 17.12 | 10.13 |

1. *Human vision under low illumination.* Data on human vision when the level of illumination in the environment is low have especially significant implications for safety. For example, the National Safety Council reports that motor vehicle accident rates are three times higher at night than in the daytime. This difference is believed due in large part to the relatively low illumination available during nighttime driving (McFarland, Moore and Warren[18]).

Age is an important characteristic of the host in this connection. During low illumination, older persons require more light to see. Table 9 shows the relative intensities of illumination required to see a dimly lighted moving target by persons of different ages.

2. *Age and vision through tinted windshields at night.* An analysis of the use of tinted windshields at night affords an excellent example of the role of host-agent-environment interactions. Tinted windshields have been widely accepted, and certain advantages may be obtained in reducing the glare from bright sunlight and aiding in the control of temperature within the car. The same principle has been applied to buses, especially for passenger windows, and is being considered for use in various types of trucks. Our measurements have shown, however, that the tinted glass absorbs about 28% of the light passing through it, as compared to 12% for ordinary safety glass. With this reduction in the illumination reaching the eye, the use of tinted windshields at night requires careful evaluation in order to utilize the benefits to the greatest advantage without introducing additional hazards.

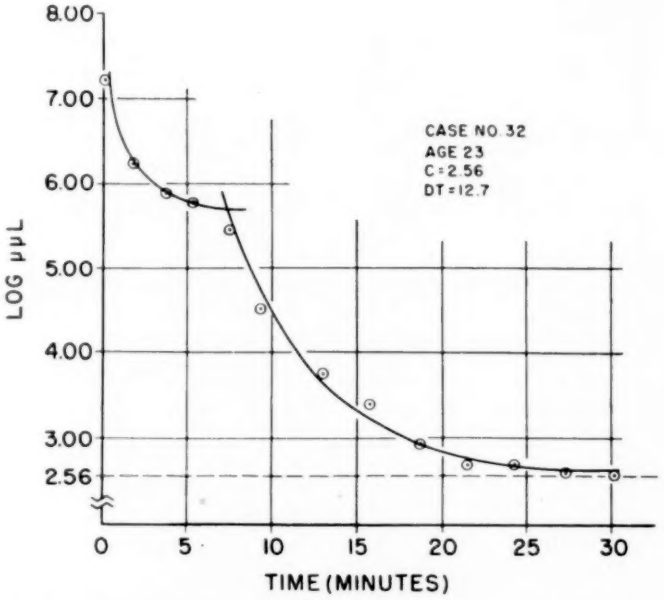


Fig. 9.—The dark adaptation curve for a typical subject. The sensitivity of the retina reaches a maximum (*c*) after a period of about 30 minutes in the dark (From McFarland and Fisher[17]).

In our research project in this area, the first step was to obtain dark adaptation curves on subjects ranging in age from 20 to 70 years. A typical curve of the course of dark adaptation is shown in Fig. 9. Figure 10 shows the scatter plot of the final adaptation levels reached in relation to age. The correlation in these data was .895, one of the highest correlations reported between age and a biological function. In practical terms this finding indicated that for a very dim light or object

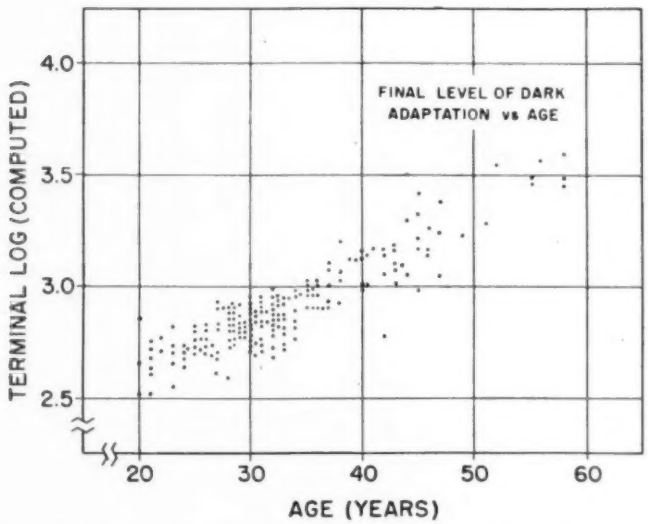


Fig. 10.—Scatter plot showing the relation of the final level of dark adaptation to age. The correlation from these data is .895, and indicates a regular decrease in sensitivity with increasing age (From McFarland and Fisher[17]).

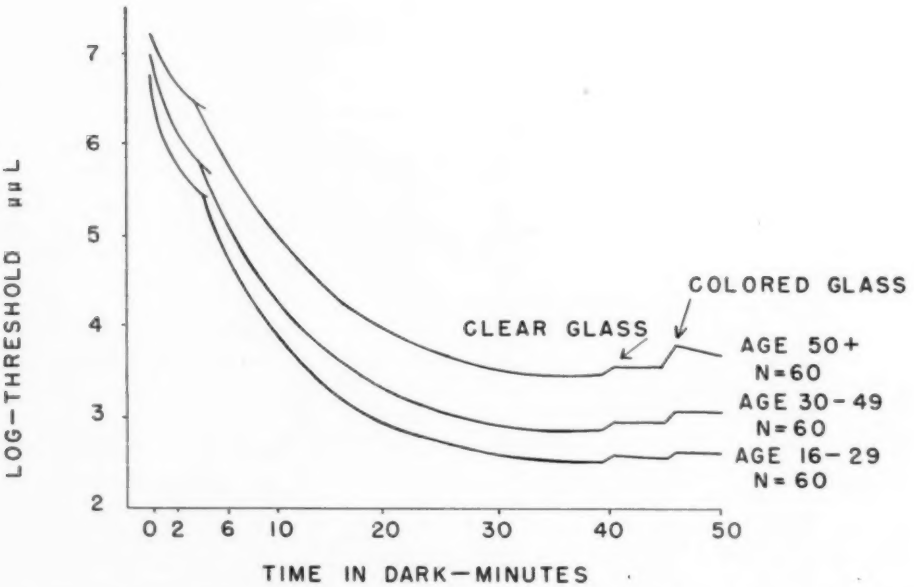


Fig. 11.—Dark adaptation in relation to age, and the effects of clear and tinted windshield glass on thresholds of sensitivity (From McFarland, Domey, Ward, and Warren[16]).

to be just seen by an eye in the dark, a doubling of the intensity of the light was required for each increase of 13 years of age (McFarland and Fisher[17]).

The next step was to obtain dark adaptation thresholds for subjects representing a wider range of ages, and to measure the effect on sensitivity thresholds when the subjects viewed the test lights through tinted windshield glass. Figure 11 shows the average dark adaptation curves for each of 3 age groups of subjects, and indicates the magnitude of the decrease in light sensitivity which occurs with increasing age.

Figure 11 shows the effect when the test lights are perceived through windshield glass. Clear glass, introduced at 41 minutes, has the effect of raising the threshold slightly. When the tinted glass was introduced, at 46 minutes, the effect was substantially greater. The practical implication of this finding is that at any age, dimly lighted objects which are just perceptible through clear windshields, will not be perceptible through the tinted windshields. When the effects of both the tinted glass and increasing age are compounded, the difference is very marked (McFarland, Domey, Ward and Warren[16]).

The final part of this project will be to run tests on the highway at twilight and at night, with and without tinted windshields. The objects to be seen by the subjects will be located at places unknown to them. Although the evidence from these and other studies may indicate that subjects over 55 or 60 may experience difficulty in driving at night with tinted windshields, certain precautions may be developed which might limit the hazards and retain the advantages of this design feature. Obviously, the relative density of the glass at the eye level height of drivers, and the spectral transmission characteristics of the filter are both important considerations.

3. *The influence of exposure to low concentrations of carbon monoxide.* The influence of environmental factors upon human performance may be very subtle, and one final example may be given. Carbon monoxide is a toxic gas which at times is of considerable importance in the environment of driving, as well as in many industrial situations. In concentrations well below those known to be dangerous to life, exposure to this gas may have a deleterious effect on the efficiency of certain human reaction systems. For instance, the eye becomes less sensitive at low illuminations with very small quantities of carbon monoxide in the blood stream. This is shown in Fig. 12, which demonstrates the reduction in night vision resulting from the carbon monoxide inhaled while smoking three cigarettes. The amount of carboxyhemoglobin formed is sufficient to reduce the supply of oxygen in the retinal and nervous tissues to that which would prevail at an altitude of 7,000 to 8,000 feet. A measurable decrement in light sensitivity can be found at altitudes as low as 5,000 feet. Such data are especially significant when it is appreciated that CO, altitude, and other variables influencing the supply and transport of oxygen are additive in their effects, and in combination may produce serious states of oxygen deficiency, with marked effects upon performance and safety (McFarland *et al.*[20]).

**Summary and Conclusions.** 1. It has been brought out in this discussion that accidental trauma has reached epidemic proportions among our civilian and military populations. Accidents, particularly those occurring in industry, on the highway and in our homes, now constitute the outstanding threat

to the health and productive resources of the nation.

2. The thesis has been developed that the control of this threat to health and safety falls within the province of preventive medicine, and that the medical officer and physician have as much responsibility for the prevention of accidental death and injury as for the prevention and treatment of disease.

3. It has been proposed that the epidemiological approach originally developed for the control and study of mass infectious disease is also applicable to the study and control of accidental trauma. Similar biological laws are involved, and because of the multiple causes of accidents, a team-approach is a basic requirement.

4. In this view accidents are considered to result from the interactions of three different factors: 1) the host (the soldier, worker, or driver), 2) the agent (or equipment) and 3) the environment. The host is of primary medical concern, and the physician, because of his knowledge of the characteristics of the host, is in an especially advantageous position to contribute to the analysis of accident causes, and to educate in safety while treating.

The interactions between the host and the agent and the environment must also be considered in developing effective measures for accident prevention. The first step in such a program is the description of the anatomical, physiological, and psychological characteristics of the host. When these data are related to the agent under specific environmental conditions, information will be obtained which will be useful in developing sound, preventive programs.

5. While particular characteristics of the host have not been shown to be invariably connected with accidents, a number of useful principles have been developed. One most important working rule is that the job to which a person is assigned should be related to his behavioral, psychological, and physical characteristics. The influence on safety of various temporary states in the individual, such as fatigue, emotional problems, and the effects of alcohol, cannot be overemphasized.

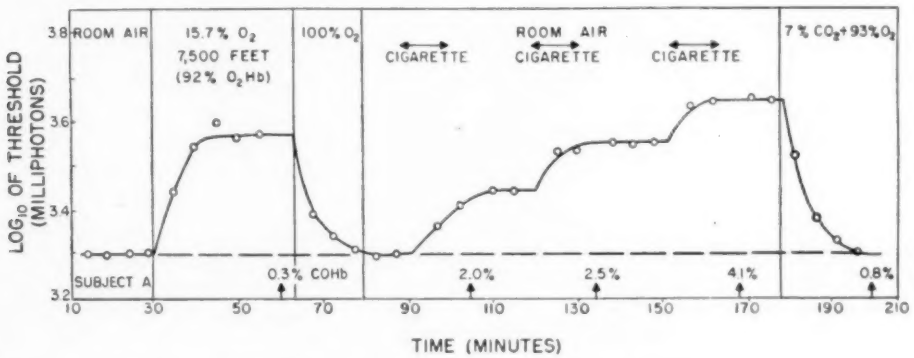


Fig. 12.—The reduction in night vision due to carbon monoxide from cigarette smoke. The figure compares the loss in light sensitivity due to the CO in the smoke from three cigarettes with the effect of the anoxia of high altitude
(From McFarland, Roughton, Halperin and Niven[20]).

Methods of detecting the accident repeater in advance have not yet been perfected, but the most promising approach is based on the concept that "a man works (or drives) as he lives." At the very least, medical officers and industrial physicians can identify them with a record of repeated accidents, and through clinical approaches determine how well adapted they are to their jobs and responsibilities.

6. One important way of improving safety is by the design of equipment in terms of human capabilities and limitations. This involves the closer integration of the host-agent relationships through the application of the principles of human engineering. Such an approach utilized in conjunction with an advance analysis of possible faults in the design of the equipment can aid substantially in the reduction of accidents.

7. The third phase of the epidemiological approach or the host-environment relationship is concerned with the effect of the physical variables on the individual. Such factors as the level of illumination, the temperature and humidity, noise, and the like, are of importance here. For each of these variables there are reasonably well defined zones of comfort and discomfort, and ranges where the efficiency of human performance is reduced to the detriment of safety.

8. In conclusion, the premise which I have attempted to develop is that accidental trauma is now a major problem in the field of preventive medicine and public health. Since human factors play a predominant role in their causation, the medical officer, with his thorough training in the biological and psychological phases of human behavior, has an important responsibility in the control and prevention of accidents. There is an urgent need for the physician, working closely with other specialists in related fields, to make carefully controlled experimental and clinical studies, epidemiological surveys, and statistical analyses in order to conserve and strengthen the health and safety of our people.

9. Finally, to return again to another quotation from T. S. Eliot which describes so vividly the purpose of scientific investigation:

> "We shall not cease from exploration
> And the end of all our exploring
> Will be to arrive where we started
> And know the place for the first time."[4]

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## SUMMARIO IN INTERLINGUA

### Le Rolo de Factores Human in Trauma Accidental

1. Trauma accidental ha attingite proportiones epidemic in le population civil e militar. Accidentes, specialmente accidentes que occurre in fabricas, autostratas, e nostre domicilios, representa a iste tempore le major menacia pro le sanitate e le ressources productive del nation.

2. Le subjugation de iste menacia al sanitate e securitate del population es un problema que debe concerner le medicina preventive. Su responsabilitate pro le prevention de mortes e vulneres accidental non es minus grande que su responsabilitate pro le prevention e le tractamento de morbos.

3. Le conceptos e attitudes epidemiologic que esseva originalmente disveloppate pro le subjugation e le studio de morbos infectiose es etiam applicabile al studio e al subjugation de trauma accidental. Le leges biologic es le mesmes in le duo situationes, e le multiplicitate del causas de accidentes establi le necessitate fundamental de methodos cooperative.

4. Accidentes resulta del interaction de tres distincte factores: (1) Le hospite (*i.e.* le humano), (2) le agente (o le apparatura), e (3) le milieu. Le hospite es de interesse primari ab le puncto de vista medical, e le medico, a causa de su cognoscentias in re le characteristicas del hospite, es le melio qualificate a

contribuer al analyse del causas de accidentes e a educar le patiente in le principios de securitate durante que ille le tracta.

Le interaction de hospite, agente, e milieu debe etiam esser prendite in consideration in le disveloppamento de mesuras de prevention de accidentes. Le prime passo in un tal programma es le description del characteristicas anatomic, physiologic, e psychologic del hospite. Quando iste datos es relationate al agente sub le conditiones de un milieu particular, on obtene informationes que es de valor pro le disveloppamento de un efficace programma de prevention.

5. Ben que il non ha essite demonstrate que characteristicas particular del hospite es invariabilemente connectite con accidentes, un numero de principios de valor ha essite disveloppate: Le typo de labor a que un individuo es deputate debe esser correlationate con su characteristicas comportamental, psychologic, e physic. Le influentia que es exercite super le securitate per varie statos temporari del individuo, per exemplo fatiga, problemas emotional, e le effectos de alcohol, non pote esser exaggerate. Methodos pro le detection a priori de repetentes de accidentes ha non ancora essite perfectionate, sed un base promittente es fornite per le concepto que "un homine travalia (o manipula un vehiculo) como ille vive." Al minus, functionarios medical e medicos industrial pote identificar tal repetentes de accidentes super le base de lor historias, e per methodos de analyse clinic illes pote determinar a qual grado le individuos in question es adaptabile a lor travalio e lor responsabilitates.

6. Un methodo importante pro le promotion de securitate es le construction e disposition del equipamento mechanic in consideration del capabilitates e limitationes human. Isto es un question de un plus immediate integration del relationes inter hospite e agente per le application del principios de ingenieria human e un planation meliorate del equipamento mechanic.

7. Le tertie phase del methodologia epidemiologic se occupa del effecto que es exercite super le individuo per variabiles physic, per exemplo le qualitate del illumination e le stato de temperatura, humiditate, e factores acustic, etc. Pro omne iste variabiles il existe satis ben-definite zonas de conforto e disconforto e areas in que le efficacia del functionamento human es reducite al detrimento del securitate.

8. Le medico del tempore presente e del futuro pote haber un rolo importante in le prevention de accidentes. Progressos significative es a expectar ab controlate studios experimental e clinic, investigationes epidemiologic, e analyses statistic e ab intime formas de collaboration inter medicos e altere specialistas biologic, ingenieros, e functionarios administrative.

# THE TREATMENT OF THE ACUTE ASTHMATIC ATTACK WITH AN ORAL ALCOHOL-WATER SOLUTION OF THEOPHYLLINE (ELIXOPHYLLIN)*

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Theophylline ethylenediamine (Aminophylline USP) administered intravenously has been shown to be effective in terminating paroxysms of asthma by many authors. However, in addition to the inconvenience of the intravenous route of administration, untoward reactions are not infrequent and occasional fatalities have been noted with this method of administration.

Previous study by two of us (J.S. and J.T.M.) demonstrated that theophylline appeared in the blood rapidly and in high concentration following the administration of 75 ml. of an alcohol-water solution of theophylline (Elixophyllin). Significant blood levels were reached 15 minutes after ingestion and were considerably higher than the levels attained after the administration of either Aminophylline or Choline Theophyllinate tablets. Because of this demonstration of enhanced absorbability of theophylline when dissolved in an aqueous-alcoholic medium, the following clinical investigation was undertaken.

The purpose of this study was to evaluate the efficacy of an oral alcohol-water solution of theophylline in terminating acute asthmatic attacks.

**Material and Method.** Fifty unselected patients who presented themselves at the Emergency Room of The Long Island College Hospital for treatment of an acute asthmatic attack were utilized for the purpose of this study. There were 24 males and 26 females in this group. Ages ranged from 17 to 67 years.

After preliminary examination and confirmation of the diagnosis of asthma by the characteristic auscultatory findings, each patient was given 60 to 75 ml. of the alcohol-water solution of theophylline to drink in a single dose. This preparation contains 20% ethyl alcohol and 80 mg. theophylline per 15 ml. The total dose administered was equivalent to 400 mg. of theophylline or 500 mg. of Aminophylline. The patients were observed for beneficial effects and the lungs ausculted when improvement was reported by the patient. The interval between administration of the medication and subjective relief was noted. If no benefit was noted after 30 minutes had elapsed, the medication was considered to have been ineffective. Those patients who did not benefit or who obtained insufficient relief were then treated with Adrenalin or intravenous Aminophylline, or both.

**Results.** (Table 1.) Of the 50 individual asthmatic attacks treated, 37 (74%) responded with complete relief and were discharged from the Emergency Room without further treatment. Five patients (10%) obtained incomplete relief and further treatment with

*Elixophyllin—Sherman Laboratories.

TABLE 1.—RESULTS OF ORALLY ADMINISTERED ALCOHOL-WATER SOLUTION OF THEOPHYLLINE IN 50 CASES OF ACUTE ASTHMA

| *Subject* | *Sex* | *Age* | *Results* | *Additional Treatment* | *Hospitalization Required* |
|---|---|---|---|---|---|
| D.A. | F | 20 | Complete Relief | | No |
| I.F. | M | 47 | Complete Relief | | No |
| E.R. | M | 66 | No Relief | I.V. Aminophylline | Yes |
| J.B. | F | 27 | Complete Relief | | No |
| S.U. | M | 52 | Complete Relief | | No |
| A.C. | F | 50 | Complete Relief | | No |
| T.M. | M | 41 | Complete Relief | | No |
| N.M. | F | 57 | No Relief | I.V. Aminophylline | Yes |
| G.D. | F | 29 | Incomplete Relief | Adrenalin | No |
| R.F. | M | 45 | Complete Relief | | No |
| B.J. | F | 56 | Complete Relief | | No |
| F.E. | F | 25 | Complete Relief | | No |
| Y.R. | F | 28 | Complete Relief | | No |
| T.M. | F | 63 | Complete Relief | | No |
| J.C. | F | 34 | Complete Relief | | No |
| J.M. | F | 26 | Complete Relief | | No |
| M.O. | F | 40 | Complete Relief | | No |
| A.D. | F | 35 | Complete Relief | | No |
| L.M. | F | 48 | Complete Relief | | No |
| L.C. | M | 46 | No Relief | I.V. Aminophylline | No |
| T.M. | F | 24 | Complete Relief | | No |
| A.F. | F | 29 | Complete Relief | | No |
| A.D. | F | 35 | Complete Relief | | No |
| N.S. | F | 26 | No Relief | I.V. Aminophylline | No |
| C.D. | F | 42 | Complete Relief | | No |
| W.B. | M | 45 | Complete Relief | | No |
| A.C. | F | 41 | Complete Relief | | No |
| M.D. | M | 38 | Incomplete Relief | Adrenalin | No |
| E.U. | M | 27 | Complete Relief | | No |
| F.C. | M | 27 | No Relief | Adrenalin | Yes |
| D.B. | M | 28 | Complete Relief | | No |
| N.S. | M | 41 | Complete Relief | | No |
| D.P. | M | 50 | Complete Relief | | No |
| J.R. | F | 20 | Incomplete Relief | Adrenalin and I.V. Aminophylline | No |
| A.F. | M | 65 | Complete Relief | | No |
| D.F. | M | 17 | Complete Relief | | No |
| A.S. | M | 55 | Complete Relief | | No |
| L.S. | M | 53 | Complete Relief | | No |
| D.F. | M | 17 | Complete Relief | | No |
| L.M. | F | 55 | No Relief | Adrenalin and I.V. Aminophylline | No |
| M.W. | F | 35 | Complete Relief | | No |
| S.B. | M | 67 | Incomplete Relief | Adrenalin and I.V. Aminophylline | No |
| H.J. | M | 42 | No Relief | I.V. Aminophylline | Yes |
| M.Q. | M | 44 | Incomplete Relief | Adrenalin | No |
| P.H. | F | 33 | No Relief | Adrenalin and I.V. Aminophylline | No |
| D.P. | M | 33 | Complete Relief | | No |
| A.L. | M | 42 | Complete Relief | | No |
| A.R. | F | 38 | Complete Relief | | No |
| E.C. | F | 34 | Complete Relief | | No |
| D.F. | M | 17 | Complete Relief | | No |

Adrenalin or Aminophylline, or both, was necessary. Eight patients (16%) did not respond at all to the oral alcohol-water solution of theophylline. Of these, 4 did not respond to intravenous Aminophylline or Adrenalin and had to be admitted to the hospital for the treatment of status asthmaticus.

Although not noted in Table 1, one patient complained of abdominal pain and vomited following the ingestion of the medication.

DISCUSSION. The xanthine compounds have a well established place in the treatment of asthma; when used intravenously, their effects are often dramatic. The use of xanthines orally in the treatment of acute asthma has been limited by the slowness of action and the inability to attain sufficiently high blood levels without severe gastrointestinal side effects. Schluger, McGinn and Hennessy[1] demonstrated that when an aqueous-alcoholic solution of theophylline was administrated orally in a dose of 2½ ounces, high blood theophylline levels were obtained promptly (within 15 to 30 minutes). The blood levels attained were higher than those found by Waxler and Schack[2] after the administration of 250 mg. of Aminophylline intravenously or 500 mg. Aminophylline intramuscularly. It is believed that the rapid absorption is aided by the presence of the theophylline in a liquid medium which disperses the theophylline over a large area of gastrointestinal mucosa, and also the alcoholic content is thought to induce prompt absorption of the theophylline.

**Summary.** The oral administration of 60 to 75 ml. of an alcohol-water mixture (20% ethanol) containing in solution 80 mg. of theophylline per 15 ml. to 50 patients with acute asthma successfully terminated the attacks in 37 (74%). Four of the 13 patients who obtained incomplete or no relief were in status asthmaticus and required hospitalization. When the single-dose method was employed, there were very few gastrointestinal side effects.

The therapeutic advantages of an effective xanthine preparation for the treatment of acute asthma which avoids the intravenous or intramuscular routes are obvious.

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## SUMMARIO IN INTERLINGUA

### Le Tractamento de Acute Attaccos Asthmatic per Medio del Administration Oral de un Solution de Theophyllina (Elixophyllina) in un Medio Aquose-Alcoholic

Le administration oral de 60 a 75 ml de un mixtura aquose-alcoholic (20 pro cento ethanol) continente 80 mg de theophyllina per 15 ml resultava in 37 ex 50 casos de acute attaccos asthmatic (74 pro cento) in le termination del episodio. Quatro del 13 patientes qui obteneva incomplete grados de alleviamento o nulle alleviamento del toto esseva in stato asthmatic e requireva hospitalisation. Quando le methodo a dose unic esseva usate, le incidentia de adverse effectos gastrointestinal esseva bassissime.

Non es necessari sublinear le avantages therapeutic de un efficace preparato xanthinic que evita le via intravenose o intramuscular in le tractamento de asthma acute.

# THE LIMITED USE OF CHLORPROMAZINE IN BRONCHIAL ASTHMA*

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It has been reported that chlorpromazine is of value in the treatment of acute bronchial asthma (Ende[1] and Mayer, Kinson-Wright and Finney[3]). In an effort to evaluate the drug's usefulness, a group of 7 asthmatic subjects and 7 normal controls were given this drug intravenously and studied with closed-system spirometry.

**Methods.** Three normal females, 4 normal males, 4 asthmatic females and 3 asthmatic males were selected. The asthmatic patients all had highly reversible disease, a strongly allergic family history and were being currently treated for pollen and dust sensitivity.

The subjects were placed in a horizontal position and rebreathed from a closed-system recording on variable speed kymographs. A flow of oxygen into the system was supplied to replace that taken up by the subject and a $CO_2$ scrubber removed carbon dioxide. Infusions were given into an antecubital vein, and the blood pressure, pulse, intermittent electrocardiographs, minute ventilation and intermittent maximal expiratory efforts were recorded. After an infusion of saline had been given for 15 to 30 minutes as a control, a solution containing 15 to 25 mg. of chlorpromazine in 250 ml. was substituted by means of a Y tube without the knowledge of the subject. The flow was adjusted to 100 drops per minute and the entire volume was given in a period of 15 to 20 minutes. Fourteen such infusions were given without difficulty.

**Results.** The following observations were made in the 7 normal and 7 asthmatic subjects as recorded in Tables 1 and 2.

a. PULSE RATE. Six of the 7 normal subjects exhibited a rise in pulse rate of 10 to 25 beats per minute. The remaining subject had a fall of 25 beats. In 3 of the 7 asthmatic subjects, the pulse rate rose 10 to 40 beats per minute. It remained unchanged in 3 and fell in one subject.

b. BLOOD PRESSURE. In 6 of the 7 normal subjects, the blood pressure fell slightly. In the remaining subject there was a slight rise. In 5 of the 7 asthmatic patients there likewise was a fall and in the remaining 2 subjects there was no change.

c. RESPIRATORY RATE. In 5 of the 7 normal and asthmatic subjects, the respiratory rate rose. In one subject in each group it remained unchanged and in one it decreased.

d. TIDAL VOLUME. The tidal volume decreased in 6 of 7 patients in each group. It remained unchanged in one normal subject and rose in one asthmatic patient.

*This study was aided in part by a grant from Smith, Kline & French Laboratories, Philadelphia, Pennsylvania; and in part by U.S. Public Health Service Grant M609.

TABLE 1.—EFFECTS OF CHLORPROMAZINE GIVEN INTRAVENOUSLY TO SEVEN PATIENTS WITH ASTHMA

| *Asthmatic Patients* | *Pulse* | *Blood Pressure* | *Tidal Vol./ml.* | *Resp./min.* | *Minute Ventilation L./min.* | *Total Vital Capacity* | *1st Sec. Vol.* | *Symptoms* | *Effects* |
|---|---|---|---|---|---|---|---|---|---|
| EW | 90–100* | 120/70 | 500 | 16 | 8.0 | 2000 | 1300 | | |
| ♂ 27 | 130* | 110/70 | 400 | 23 | 9.2 | 2050 | 1650 | | |
| | 130* | 112/70 | 375 | 24 | 9.0 | 2100 | 1800 | | Patient very sleepy |
| | | | | | | (2400) | (1890)† | | |
| AG | 83 | 122/80 | 700 | 12 | 8.4 | 2850 | 1200 | Chest heavy | |
| ♂ 26 | 75 | 142/80 | 400 | 16 | 6.4 | 2300 | 1100 | Similar to asthma | |
| | 75 | 128/76 | | | | 2300 | 1300 | (After amino.) | Sleepy |
| | | | | | | (3500) | (2100) | | |
| RR | 100 | 115/100 | 500 | 34 | 17.0 | 2400 | 1300 | | |
| ♂ 26 | 110 | 110/80 | | | | 1800 | 1100 | | |
| | 110 | 130/80 | 500 | 30 | 15.0 | 1200 | 800 | Coughing | No drowsiness |
| | | | | | | (3100) | (2100) | | |
| JE | 110 | 160/100 | 900 | 16 | 14.4 | 3200 | 1600 | | Drowsy |
| ♂ 39 | 150 | 160/90 | 700 | 24 | 16.8 | 3500 | 2000 | | Dopiness |
| | 150 | | | | | 3600 | 2000 | | |
| | | | | | | (4500) | (4000) | | |
| ES | 100 | 100/70 | 700 | 14 | 9.8 | 4200 | 2200 | | |
| ♂ 21 | 110 | | | | | 3900 | 1700 | Sleeping | Nose stuffy |
| | 100 | 96/70 | 400 | 30 | 12.0 | 3100 | 1700 | Wheezing | Sleepy, dopey |
| | | | | | | (4600) | (4000) | | |
| JC | 75 | 120/80 | 700 | 11 | 7.7 | 3250 | 2150 | Warmness | No great drowsiness |
| ♂ 43 | 75 | | | | | 3850 | 2890 | Tightness in chest | (drowsy 12 hrs. later) |
| | 75 | 138/80 | 600 | 11 | 6.6 | 3900 | 2900 | Tingling | |
| | | | | | | (4500) | (3500) | | |
| WK | 65 | 130/80 | 500 | 19 | 9.5 | 2250 | 1100 | | Extremely drowsy |
| ♂ 39 | 65 | 112/80 | 350 | 24 | 8.4 | 2500 | 1000 | | |
| | 65 | | 450 | 24 | 10.8 | 2750 | 1100 | | |
| | | | | | | (3500) | (1800) | | |

* At 0, 10, 20 min.
† Best observed VC and 1st second volume in 36 months of repeated observation

TABLE 2.—EFFECTS OF CHLORPROMAZINE GIVEN INTRAVENOUSLY TO SEVEN NORMAL INDIVIDUALS

| *Normal Subjects* | *Pulse* | *Blood Pressure* | *Tidal Vol./ml.* | *Resp./min.* | *Minute Ventilation L./min.* | *Total Vital Capacity* | *1st Sec. Vol.* | *Symptoms* | *Effects* |
|---|---|---|---|---|---|---|---|---|---|
| SS | 75 | 140/80 | 400 | 24 | 9.6 | 3250 | 3000 | | |
| ♂ 23 | 100 | 132/72 | 300 | 32 | 9.6 | 3400 | 3000 | | |
| | 75 | 134/80 | 300 | 32 | 9.6 | 3300 | 3000 | Stuffy nose | Drowsy and sleepy to 12 hrs. after |
| PR | 60–75 | 116/70 | 350 | 27 | 9.4 | 3400 | 2900 | | Not noticeably drowsy |
| ♂ 30 | 75 | 136/82 | 375 | 23 | 8.6 | 3700 | 3100 | | Worse 2 hrs. later |
| | 75 | | 325 | 23 | 7.5 | 3700 | 3100 | | Very sleepy 8–12 hrs. |
| MH | 100 | 125/75 | 1100 | 18 | 19.8 | 2900 | 2400 | | |
| ♂ 25 | 90–100 | 110/58 | 450 | 18 | 8.1 | 3000 | 2600 | Sleeping | Sleeping |
| | 90–100 | | 420 | 20 | 8.4 | 3000 | 2600 | Extremely drowsy | Very sleepy, drowsy for 12 hrs. |
| HF | 125 | 136/80 | 280 | 23 | 6.4 | 3900 | 3200 | | |
| ♂ 21 | 100 | 130/76 | 230 | 30 | 6.9 | 4000 | 3800 | | |
| | 100 | 130/78 | 230 | 30 | 6.9 | 3700 | 3400 | None | Stuffy nose, drowsy |
| SA | 60–75 | 120/76 | 600 | 16 | 9.6 | 3600 | 3200 | | Stuffy nose |
| ♂ 25 | 75–80 | 120/70 | 550 | 26 | 14.3 | 3600 | 3200 | None | Sensation of easier breathing |
| | 75 | | | | | 3300 | 2600 | | |
| GS | 75 | 120/80 | 1100 | 12 | 13.2 | 3100 | 2700 | | |
| ♂ 26 | 108 | 100/70 | 1000 | 12 | 12.0 | 3200 | 2700 | | |
| | 83 | 110/70 | 1000 | 12 | 12.0 | 3200 | 2700 | None | None |
| GSp | 75 | 130/70 | 450 | 34 | 15.3 | 4200 | 4100 | | |
| ♂ 11/12 | 100 | | | | | 4300 | 4050 | | |
| | 100 | 130/70 | 470 | 38 | 17.9 | 4650 | 4150 | None | None |

e. TOTAL VITAL CAPACITY. The total vital capacity decreased in 2 normal subjects and 3 asthmatic patients. It rose in 3 normal and 3 asthmatic subjects and remained unchanged in the others. The first second volume increased in 3 subjects in each group, decreased in one normal and 2 asthmatics, and was unchanged in the remainder.

f. ELECTROCARDIOGRAPHIC CHANGE. There was slight flattening of the T-waves in the precordial leads in 2 subjects in each group.

As described above and as noted in Tables 1 and 2, there appears to be no significant difference between either the normal or asthmatic subject after the administration of intravenous chlorpromazine in doses of 15 to 25 mg. given over a 15- to 30-minute period. Although anxiety, restlessness and apprehension may be relieved by this drug (which consistently produced a sleepy, drowsy relaxed state in the subjects studied) no objective evidence of effective bronchodilation was apparent. Indeed, 2 patients with bronchial asthma had increased symptoms after study. These symptoms were rapidly improved with intravenous aminophylline.

**Discussion.** Sedation alone will often decrease the subjective difficulties associated with an acute asthmatic attack, perhaps in part because sedation may be accompanied by a decrease in the minute volume. The effect will then be to decrease audible wheezing and auscultatory signs (Lowell[2]). This will diminish anxiety in the subject and tend to give the physician a false sense of security because the same degree of diffuse bronchiolar obstruction may still persist but be less evident. Sedation was the only consistent effect observed in these studies, perhaps desirable under some circumstances but one which is not directed at the basic problem in the acutely ill asthmatic patient. Our results would indicate, therefore, that an effective bronchodilator would have to be used in addition to chlorpromazine in the treatment of bronchial asthma.

**Summary.** Seven asthmatic patients and 7 normal controls were studied by closed-system spirometry in an effort to evaluate the usefulness of chlorpromazine given by intravenous infusion for bronchial asthma. No consistent subjective relief or evidence of bronchodilator effect was noted, although sedation was marked. Two asthmatic patients had increased symptoms immediately after the infusion.

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## SUMMARIO IN INTERLINGUA

### Le Utilitate Restringite de Chlorpromazina in Asthma Bronchial

Un gruppo de 7 subjectos nonasthmatic e un gruppo de 7 patientes con asthma esseva studiate per spirometria a systema claudite con le objectivo de evalutar le utilitate de chlorpromazina in asthma bronchial. Le droga esseva administrate in doses de 15 a 25 mg per via intravenose durante periodos de 15 a 30 minutas. Anxietate, disquietude, e apprehension esseva alleviate per le droga. Marcate grados de sedation esseva evidente, sed nulle evidentia subjective o objective de un regular effecto bronchodilatatori esseva notate. Duo patientes habeva augmentate symptomas post le infusion.

# TOBACCO SMOKING AND AUTOMOBILE-DRIVING STRESS IN RELATION TO DEATHS FROM CARDIAC AND VASCULAR CAUSES

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Ten years ago we carried out a survey[2] which showed an association between tobacco smoking and coronary heart disease of such mathematical significance as to be well beyond the range of chance occurrence. At that time publication space could not be found in a medical journal of wide circulation, so the significant statistical findings of that survey are recapitulated here in their relation to the results of our newer and broader study.

Table 1 presents the essential features of our 1946–1947 survey of the smoking habits of 484 white males dying of coronary occlusion in Cincinnati and of some 1,147 white male controls interviewed in all census tracts of Columbus, Ohio[4].

"All male coronary victims under 41 years of age were cigarette smokers and all but 1 under 46 years! The percentage of cigarette smokers among coronary victims is significantly higher than normal up to age 60, while after this age the incidence of pipe and cigar smoking is abnormally high. Tobacco smoking in some form is thus abnormally prevalent among all ages of coronary victims and the percentage of nonsmokers significantly below normal."

Within the past year (1956) we have completed a broader and more detailed survey of smoking habits in white living populations with respect to age, sex, place of residence and annual motor driving mileage. The survey findings on the living populations have been compared with similar information on those dying of respiratory tract cancer and diseases of the heart and vessels. The details of the living-population and lung cancer death survey are being presented elsewhere for those with long-term (10 years or more) residence in the given area[5]. With lung cancer we are particularly interested in a) the amounts of tobacco smoked, b) the doubling or trebling of this tobacco smoking effect by annual urban driving mileages of 12,000 miles or more, and c) the still further doubling of these combined exacerbating influences by residence in an area of almost constant general air pollution.

This survey has just now been extended to cover cardiac and vascular disease deaths (International List of Causes of Death, 420–2, 430–4, 440–7, 450–6), again in association with tobacco smoking and the additional exacerbating stress effects of high annual mileages of urban driving and of residence in crowded downtown areas.

Table 2 indicates the actual numbers of male white individuals surveyed in each of the 3 living population groups, with classification by age, annual driving mileage, and percent-

age distribution of smoking types within each age decade (with any smoking combination including cigarettes being classed in the appropriate cigarette category). It will be noted that this 1955–1956 smoking survey shows a rise in the percentage of cigarette smokers in every age decade at the expense of the nonsmoker and pipe-cigar smoker percentages, when compared to the 1946–1947 percentage distribution in Table 1 and the more complete reports of the Columbus smoking survey[4].

Our present Ohio survey encompassed only some 2300-odd households in 3 population areas, as contrasted to almost 10 times that number covered in the 1955 nation-wide survey carried out by the Census Bureau for the Public Health Service (Haenszel, Shimkin and Miller[1]), yet there are only minor differences between their survey findings and ours:

TABLE 1.—SMOKING HABITS OF CINCINNATI CORONARY VICTIMS AND COLUMBUS LIVING RESIDENTS
(White males only 1946–1947)

| | | | *Incidence of Smoking* | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | *Nonsmokers* | | *Pipe and/or Cigars* | | *Cigarettes* | |
| *Groups* | *Ages* | *Numbers* | *%* | *PE* | *%* | *PE* | *%* | *PE* |
| Coronary | 20–9 | 2 | 0 | | 0 | | 100 | |
| Controls | 20–9 | 351 | 22.79 | | 2.28 | | 74.93 | |
| Coronary | 30–9 | 8 | 0 | | 0 | | 100 | |
| Controls | 30–9 | 190 | 22.11 | | 3.68 | | 74.21 | |
| Coronary | 40–9 | 56 | 7.14 | ±2.30 | 8.93 | ±2.58 | 83.93 | ±3.30 |
| Controls | 40–9 | 216 | 19.91 | ±1.84 | 9.26 | ±1.31 | 70.83 | ±2.08 |
| Diff/PE Diff | | | 12.77 | =4.3 | 0.33 | =0.1 | 13.10 | =3.4 |
| | | | 2.95 | | 2.89 | | 3.90 | |
| Coronary | 50–9 | 135 | 6.66 | ±1.38 | 11.11 | ±1.81 | 82.23 | ±2.23 |
| Controls | 50–9 | 188 | 24.47 | ±2.10 | 16.47 | ±1.80 | 59.94 | ±2.42 |
| Diff/PE Diff | | | 17.81 | =7.1 | 5.38 | =2.0 | 23.19 | =7.1 |
| | | | 2.51 | | 2.65 | | 3.29 | |
| Coronary | 60–9 | 153 | 18.30 | ±2.10 | 32.68 | ±2.56 | 49.02 | ±2.72 |
| Controls | 60–9 | 114 | 35.09 | ±3.01 | 21.05 | ±2.57 | 43.86 | ±3.13 |
| Diff/PE Diff | | | 16.79 | =4.6 | 11.63 | =3.2 | 5.16 | =1.2 |
| | | | 3.67 | | 3.63 | | 4.15 | |
| Coronary | 70+ | 130 | 33.84 | ±2.80 | 47.69 | ±2.96 | 18.44 | ±2.27 |
| Controls | 70+ | 88 | 54.12 | ±3.58 | 29.41 | ±3.26 | 16.47 | ±2.63 |
| Diff/PE Diff | | | 20.28 | =4.5 | 18.28 | =4.2 | 1.99 | =0.6 |
| | | | 4.54 | | 4.40 | | 3.47 | |

| *White Males Only* | *Ohio (20+Yrs.)* | *PHS North & West (18+Yrs.)* | *Cincinnati (20+Yrs.)* | *PHS North & West (18+Yrs.)* |
|---|---|---|---|---|
| Nonsmokers | 35.8% | 39.3% | 21.0% | 26.1% |
| Pipe or cigar, or both, only | 11.2 | 10.9 | 9.6 | 8.8 |
| Cigarettes or Comb. | 53.0 | 49.9 | 69.4 | 65.1 |

TABLE 2.—LIVING WHITE MALES SURVEYED (BY AGE DECADE, SMOKING HABITS, AND ANNUAL MILEAGE DRIVEN)

| | | | *No* | | *Pipe and* | | *<15* | | *15–35* | | *>35* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Pop.* | *Gr.* | *Driven* | *Smoking* | | *Cigars* | | *Cig./da* | | *Cig./da* | | *Cig./da* | | *Totals* | |
| *1950* | *Age* | *Mileage* | *No.* | *%* | *No.* | *%* | *No.* | *%* | *No.* | *%* | *No.* | *%* | *No.* | *%* |
| | | Cincinnati Basin Areas | | | | | | | | | | | | |
| 11628 | 30–9 | Total | 19 | 11.3 | 3 | 1.8 | 13 | 7.7 | 118 | 70.3 | 15 | 8.9 | 168 | 100.0 |
| | 30–9 | <12000 | 16 | 9.5 | 3 | 1.8 | 11 | 6.5 | 105 | 62.5 | 9 | 5.4 | 144 | 85.7 |
| | 30–9 | >12000 | 3 | 1.8 | 0 | 00 | 2 | 1.2 | 13 | 7.8 | 6 | 3.5 | 24 | 14.3 |
| 10544 | 40–9 | Total | 25 | 18.5 | 6 | 4.5 | 6 | 4.5 | 89 | 65.9 | 9 | 6.6 | 135 | 100.0 |
| | 40–9 | <12000 | 23 | 17.0 | 6 | 4.5 | 6 | 4.5 | 73 | 54.1 | 8 | 5.9 | 116 | 85.9 |
| | 40–9 | >12000 | 2 | 1.5 | 0 | 00 | 0 | 00 | 16 | 11.8 | 1 | 0.7 | 19 | 14.1 |
| 8993 | 50–9 | Total | 20 | 19.4 | 16 | 15.2 | 7 | 6.7 | 50 | 47.6 | 12 | 11.4 | 105 | 100.0 |
| | 50–9 | <12000 | 18 | 17.5 | 15 | 14.3 | 6 | 5.7 | 46 | 43.8 | 11 | 10.5 | 96 | 91.4 |
| | 50–9 | >12000 | 2 | 1.9 | 1 | 0.9 | 1 | 1.0 | 4 | 3.8 | 1 | 0.9 | 9 | 8.6 |
| 7189 | 60–9 | Total | 32 | 37.6 | 11 | 12.9 | 9 | 10.6 | 27 | 31.8 | 6 | 7.1 | 85 | 100.0 |
| | 60–9 | <12000 | 31 | 36.5 | 10 | 11.7 | 9 | 10.6 | 27 | 31.8 | 6 | 7.1 | 83 | 97.6 |
| | 60–9 | >12000 | 1 | 1.1 | 1 | 1.2 | 0 | 00 | 0 | 00 | 0 | 00 | 2 | 2.4 |
| | | Cincinnati-Suburban Areas | | | | | | | | | | | | |
| 11856 | 30–9 | Total | 16 | 11.9 | 4 | 3.0 | 14 | 10.4 | 96 | 71.1 | 5 | 3.6 | 135 | 100.0 |
| | 30–9 | <12000 | 7 | 5.2 | 2 | 1.5 | 8 | 5.9 | 72 | 53.3 | 0 | 00 | 89 | 65.9 |
| | 30–9 | >12000 | 9 | 6.7 | 2 | 1.5 | 6 | 4.5 | 24 | 17.8 | 5 | 3.6 | 46 | 34.1 |
| 12380 | 40–9 | Total | 36 | 16.2 | 15 | 6.8 | 24 | 10.8 | 136 | 61.3 | 11 | 5.0 | 222 | 100.0 |
| | 40–9 | <12000 | 28 | 12.7 | 12 | 5.4 | 19 | 8.5 | 110 | 49.6 | 6 | 2.7 | 175 | 78.8 |
| | 40–9 | >12000 | 8 | 3.5 | 3 | 1.4 | 5 | 2.3 | 26 | 11.7 | 5 | 2.3 | 47 | 21.2 |
| 11347 | 50–9 | Total | 48 | 24.7 | 22 | 11.3 | 26 | 13.4 | 92 | 47.4 | 6 | 3.1 | 194 | 100.0 |
| | 50–9 | <12000 | 42 | 21.6 | 19 | 9.8 | 24 | 12.4 | 78 | 40.2 | 2 | 1.0 | 165 | 85.1 |
| | 50–9 | >12000 | 6 | 3.1 | 3 | 1.5 | 2 | 1.0 | 14 | 7.2 | 4 | 2.1 | 29 | 14.9 |
| 7518 | 60–9 | Total | 25 | 26.6 | 21 | 22.4 | 18 | 19.2 | 27 | 28.7 | 3 | 3.2 | 94 | 100.0 |
| | 60–9 | <12000 | 19 | 20.2 | 18 | 19.2 | 17 | 18.1 | 24 | 25.5 | 3 | 3.2 | 81 | 86.2 |
| | 60–9 | >12000 | 6 | 6.4 | 3 | 3.2 | 1 | 1.1 | 3 | 3.2 | 0 | 00 | 13 | 13.8 |
| | | Ohio-Rural | | | | | | | | | | | | |
| 26900 | 30–9 | Total | 56 | 29.0 | 19 | 9.8 | 26 | 13.5 | 80 | 41.5 | 12 | 6.2 | 193 | 100.0 |
| | 30–9 | <12000 | 37 | 19.2 | 9 | 4.6 | 12 | 6.2 | 35 | 18.2 | 4 | 2.1 | 97 | 50.3 |
| | 30–9 | >12000 | 19 | 9.8 | 10 | 5.2 | 14 | 7.3 | 45 | 23.3 | 8 | 4.1 | 96 | 49.7 |
| 24787 | 40–9 | Total | 53 | 27.4 | 15 | 7.8 | 37 | 19.2 | 71 | 36.8 | 17 | 8.8 | 193 | 100.0 |
| | 40–9 | <12000 | 34 | 17.6 | 11 | 5.7 | 24 | 12.5 | 40 | 20.7 | 9 | 4.7 | 118 | 61.1 |
| | 40–9 | >12000 | 19 | 9.8 | 4 | 2.1 | 13 | 6.7 | 31 | 16.1 | 8 | 4.1 | 75 | 38.9 |
| 22043 | 50–9 | Total | 53 | 30.0 | 30 | 16.9 | 38 | 21.5 | 43 | 24.3 | 13 | 7.3 | 177 | 100.0 |
| | 50–9 | <12000 | 38 | 21.5 | 20 | 11.3 | 26 | 14.7 | 25 | 14.1 | 7 | 3.9 | 116 | 65.5 |
| | 50–9 | >12000 | 15 | 8.5 | 10 | 5.6 | 12 | 6.8 | 18 | 10.2 | 6 | 3.4 | 61 | 34.5 |
| 18890 | 60–9 | Total | 73 | 47.1 | 31 | 20.0 | 29 | 18.7 | 16 | 10.3 | 6 | 3.9 | 155 | 100.0 |
| | 60–9 | <12000 | 60 | 38.7 | 27 | 17.4 | 27 | 17.4 | 12 | 7.7 | 4 | 2.6 | 130 | 83.9 |
| | 60–9 | >12000 | 13 | 8.4 | 4 | 2.6 | 2 | 1.3 | 4 | 2.6 | 2 | 1.3 | 25 | 16.1 |

Indicated smoking percentages within each age-decade were projected upon the area's total number of white males (left hand column) of that age to give numbers at risk in each smoking and driving category within that age decade for the rate calculations of Table 3.

The two surveys would agree even more closely if they could be brought to exactly the same age basis. Our Ohio survey began with the 20-year olds while the PHS one began at age 18 when smoking is distinctly less prevalent. Unfortunately, the PHS published tables provide no possible basis for such complete equilibration.

Table 3 presents the numbers of male white cardiovascular deaths classified by age decades (30 to 39, 40 to 49, 50 to 59), by smoking categories, and by annual motor driving mileages (<12,000 and >12,000). The 2 population areas of Cincinnati (basin and suburban) were kept separate in the survey, with the intention of throwing them together in the final rate calculations after ascertaining that the 2 areas exhibited no significant differences. Much to our surprise we found area differences of very great significance indeed, which we will discuss in a later paragraph.

Early in the course of the survey of the cardiovascular deaths, we decided to concentrate our attention on the 3 age decades from 30 to 59 years. After age 60, death diagnoses of the categories used lose much of the direct significance they carry through the earlier age decades. In order to add to our death numbers for the earlier

TABLE 3.—CINCINNATI CARDIOVASCULAR DEATHS, WHITE MALES ONLY
(420–2, 430–4, 440–7, 450–6, Int. List of Causes of Death)
(By Age, Smoking Habits and Annual Mileage Driven)

| *Pop. 1950* | *Group Age* | *Annual Mileage Driven* | *No Smoking* | | *Pipe & Cigar* | | *<15 Cig./da.* | | *15–35 Cig./da.* | | *>35 Cig./da.* | | *All Classes* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | *No.* | *Rate°* | *No.* | *Rate°* | *No.* | *Rate°* | *No.* | *Rate°* | *No.* | *Rate°* | *No.* | *Rate°* |
| Cincinnati Basin Areas (CT 1–29, 43–4, 60–1, 74, 76–8, 86–7, 90–1, 103–4). | | | | | | | | | | | | | | |
| 11628 | 30–9 | Total | 2 | 43 | 0 | | 0 | | 12 | 42 | 3 | 82 | 17(7) | 41 |
| | 30–9 | <12000 | 1 | | 0 | | 0 | | 8 | 31 | 2 | | 11 | 31 |
| | 30–9 | >12000 | 1 | | 0 | | 0 | | 4 | 124 | 1 | | 6 | 102 |
| 10544 | 40–9 | Total | 2 | 72 | 1 | | 0 | | 30 | 281 | 10 | 936 | 43(13) | 266 |
| | 40–9 | <12000 | 1 | | 1 | | 0 | | 18 | 206 | 9 | | 29 | 209 |
| | 40–9 | >12000 | 1 | | 0 | | 0 | | 12 | 624 | 1 | | 14 | 613 |
| 8993 | 50–9 | Total | 13 | 506 | 4 | 199 | 7 | 789 | 52 | 825 | 19 | 1258 | 95(34) | 717 |
| | 50–9 | <12000 | 11 | 785 | 4 | | 5 | 662 | 35 | 603 | 10 | 719 | 65 | 537 |
| | 50–9 | >12000 | 2 | 795 | 0 | | 2 | 1511 | 17 | 3537 | 9 | 7554 | 30 | 2634 |
| Cincinnati Suburban Areas (CT 45–59, 62–5, 73, 75, 79–85, 93–102, 105–9). | | | | | | | | | | | | | | |
| 11856 | 30–9 | Total | 0 | | 0 | | 5 | 101 | 5 | 15 | 2 | 117 | 12(3) | 25 |
| | 30–9 | <12000 | 0 | | 0 | | 4 | | 4 | | 1 | | 9 | 29 |
| | 30–9 | >12000 | 0 | | 0 | | 1 | | 1 | | 1 | | 3 | 19 |
| 12380 | 40–9 | Total | 4 | 107 | 1 | | 3 | 120 | 28 | 198 | 6 | 519 | 42(3) | 182 |
| | 40–9 | <12000 | 4 | | 1 | | 3 | | 17 | 148 | 2 | 321 | 27 | 148 |
| | 40–9 | >12000 | 0 | | 0 | | 0 | | 11 | 407 | 4 | 752 | 15 | 306 |
| 11347 | 50–9 | Total | 12 | 250 | 9 | 410 | 9 | 346 | 44 | 478 | 15 | 2492 | 89(15) | 485 |
| | 50–9 | <12000 | 10 | 239 | 5 | 263 | 7 | 291 | 31 | 397 | 9 | 4635 | 62 | 374 |
| | 50–9 | >12000 | 2 | 332 | 4 | 1374 | 2 | 1031 | 13 | 930 | 6 | 1469 | 27 | 932 |

°Rates—deaths per year per 100,000 white males of specified category at risk.
Deaths of 1951–5 (5 yrs.) for 30 to 39 yr. decade, of 1954–5 (2 yrs.) for 40 to 49 yr. and 50 to 59 yr. decades.
Numbers in parentheses (rt. column) indicate deaths with incomplete survey history.

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Although our living-population survey covered a rural-farm group, as well as Cincinnati basin and suburban groups, this rural phase of the cardiovascular death survey has not yet been carried out. Its completion will probably yield information of value, since motor driving mileages are there much greater (although in less congested traffic). The over-all cardiovascular death rate is sharply lower in Ohio's rural areas than in the cities, however, hence the wisdom of eventually carrying our rural survey on to completion.

Inspection of Table 3 shows that, for the 30 to 59-year age decades of white men, 1) cardiovascular death rates rise sharply with advancing age (a well-known fact), 2) they rise sharply also with increasing cigarette usage within each age decade, 3) they are sharply higher in all age decades and smoking categories (with one single exception) for those men with an annual driving mileage above 12,000 miles than for those with a lesser mileage, and 4) they average sharply higher for basin men of every age decade and smoking category than for analogous segments of the suburban population.

Without regard to driving or smoking habits, over-all cardiovascular death rates for basin white men are higher than for suburban white men, by 64% for those in the 30 to 39-year age decade, by 46% for those in the 40 to 49-year age decade, and by 57% for those in the 50 to 59-year age decade. Beyond age 60 this difference largely disappears, the basin rate being only 2% higher than the suburban for white men in the 60 to 69-year age decade. This difference shows up in both "light" and "heavy" drivers, even though the "light" drivers among basin men average less than half the annual driving mileage covered by "light" drivers among suburban men. There would thus seem to be one or more environmental factors of basin life other than driving and tobacco smoking acting to accentuate cardiovascular death rates. Such basin environmental factors seem to be associated with large percentage death increases superimposed upon any rate exacerbations shown to be associated with driving or smoking habits.

Here, as with our lung cancer survey[5], tobacco smoking habits seem to bear the major relationship to death rates, with "heavy" motor driving and basin residence each showing an independent multiplying effect on rates in each smoking category.

Although the marked differences in death rates shown in Table 3 cannot be subjected to tests for mathematical significance, standard tests are available to demonstrate clear mathematical significance for the accompanying differences in smoking and driving habits. Chi-square tests for significance have been applied to the surveyed living population and cardiovascular death frequencies recorded in Tables 2 and 3 for basin and suburban white men age 30 to 59 years. Cigarette smoking, as compared to nonsmoking, is associated

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| Pop. 1950 | Group Age | Annual Mileage Driven | No Smoking | | Pipe & Cigar | | <15 Cig./da. | | 15–35 Cig./da. | | >35 Cig./da. | | All Classes | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No. | Rate* | No. | Rate* | No. | Rate* | No. | Rate* | No. | Rate* | No. | Rate* |
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| | 30–9 | >12000 | 0 | | 0 | | 1 | | 1 | | 1 | | 3 | 19 |
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*Rates—deaths per year per 100,000 white males of specified category at risk.
Deaths of 1951–5 (5 yrs.) for 30 to 39 yr. decade, of 1954–5 (2 yrs.) for 40 to 49 yr. and 50 to 59 yr. decades.
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age decades, we included all such deaths during a 2-year period (1954–1955) for the 40 to 49 and 50 to 59 year age decades and during a 5-year period (1951–1955) for the 30 to 39 year age decade. Before rate calculation, deaths in each age decade for which contact could not be established for filling out the questionnaire were distributed proportionately within the age decade group the same as was found for those with full survey history. In only 2 cases could we satisfactorily establish that the listed deaths belonged properly in a noncardiovascular category, although no particular effort was made by us except in the minor percentage of cases with adequate hospital records.

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Inspection of Table 3 shows that, for the 30 to 59-year age decades of white men, 1) cardiovascular death rates rise sharply with advancing age (a well-known fact), 2) they rise sharply also with increasing cigarette usage within each age decade, 3) they are sharply higher in all age decades and smoking categories (with one single exception) for those men with an annual driving mileage above 12,000 miles than for those with a lesser mileage, and 4) they average sharply higher for basin men of every age decade and smoking category than for analogous segments of the suburban population.

Without regard to driving or smoking habits, over-all cardiovascular death rates for basin white men are higher than for suburban white men, by 64% for those in the 30 to 39-year age decade, by 46% for those in the 40 to 49-year age decade, and by 57% for those in the 50 to 59-year age decade. Beyond age 60 this difference largely disappears, the basin rate being only 2% higher than the suburban for white men in the 60 to 69-year age decade. This difference shows up in both "light" and "heavy" drivers, even though the "light" drivers among basin men average less than half the annual driving mileage covered by "light" drivers among suburban men. There would thus seem to be one or more environmental factors of basin life other than driving and tobacco smoking acting to accentuate cardiovascular death rates. Such basin environmental factors seem to be associated with large percentage death increases superimposed upon any rate exacerbations shown to be associated with driving or smoking habits.

Here, as with our lung cancer survey[5], tobacco smoking habits seem to bear the major relationship to death rates, with "heavy" motor driving and basin residence each showing an independent multiplying effect on rates in each smoking category.

Although the marked differences in death rates shown in Table 3 cannot be subjected to tests for mathematical significance, standard tests are available to demonstrate clear mathematical significance for the accompanying differences in smoking and driving habits. Chi-square tests for significance have been applied to the surveyed living population and cardiovascular death frequencies recorded in Tables 2 and 3 for basin and suburban white men age 30 to 59 years. Cigarette smoking, as compared to nonsmoking, is associated

with an increased frequency of cardiovascular deaths to a significant degree in both population groups (Table 4).

*Motor Driving Mileages* above 12,000 miles per year, when compared with lesser driving mileages, are associated on the present frequency data, since the numbers of living Basin people surveyed did not bear the same proportion to the total living population of the area as prevailed in the Suburban area. It is our intention to extend

TABLE 4.

*Cardiovascular Deaths, White Men, Age 30 to 59 Years.*

| *Basin* | *Nonsmoking* | *<15 Cig./da.* | *15 to 35 Cig./da.* | *>35 Cig./da.* | *Totals* |
|---|---|---|---|---|---|
| Living | 64 | 26 | 257 | 36 | 383 |
| Deaths | 17 | 7 | 94 | 32 | 150 |
| Totals | 81 | 33 | 351 | 68 | 533 |
| | $X^2 = 15.514$ (d.f. = 3) $P<.001$ | | | | |
| *Suburban* | | | | | |
| Living | 100 | 64 | 324 | 22 | 510 |
| Deaths | 16 | 17 | 77 | 23 | 133 |
| Totals | 116 | 81 | 401 | 45 | 643 |
| | $X^2 = 29.332$ (d.f. = 3) $P<.001$ | | | | |

TABLE 5.

| *Basin Men, All Categories* | *<12,000 mi./yr.* | *>12,000 m./yr.* | *Totals* |
|---|---|---|---|
| Living | 356 | 52 | 408 |
| Deaths | 104 | 55 | 159 |
| Totals | 460 | 107 | 567 |
| | $X^2 = 37.683$ (d.f. = 1) $P<.001$ | | |
| *Suburban Men, All Categories* | | | |
| Living | 429 | 122 | 551 |
| Deaths | 98 | 45 | 143 |
| Totals | 527 | 167 | 694 |
| | $X^2 = 5.416$ (d.f. = 1) $.01<P<.02$ | | |

TABLE 6

| | *"Heavy" Drivers as Percentage of Total: Age 30 to 59 Yrs.* | | | | |
|---|---|---|---|---|---|
| | *Nonsmokers* | *Pipe & Cigars* | *<15 Cig./da.* | *15 to 35 Cig/da.* | *>35 Cig./da.* |
| Basin men | 11 | 4 | 11 | 13 | 22 |
| Suburban men | 23 | 20 | 20 | 20 | 64 |
| Rural-farm men | 33 | 38 | 39 | 48 | 52 |

to a significant degree with an increased frequency of cardiovascular deaths in both population groups (Table 5).

Whether basin vs. suburban environment bears a significant relation to cardiovascular death frequency could not be tested by the Chi-square method the survey on the Basin living population residents until proper comparison can be made between it and the Suburban.

One important point not answered by this survey is whether tobacco smoking *per se* raises cardiovascular

death rates, or whether the same restlessness leading to moderate or heavy cigarette usage also leads to cardiovascular damage. It is true that heavy cigarette smokers tend strongly to be "heavy" drivers (12,000 miles/yr.) as shown by the following breakdown (Table 6).

Obesity or other nutritional or associated disease factors cannot reasonably account for this striking basin-suburban difference in cardiovascular death rates. Nor does it seem possible to lay out any additional epidemiological approach which would significantly aid in further clarification. Since our survey results have shown a striking similarity between the death rate variations for lung cancer and those from cardiovascular causes, it was considered advisable to extend the survey to cover cancer deaths not conceivably associated with direct tissue contact with inhaled irritants or carcinogens (primary malignant tumors of the pancreas, prostate, bones and nervous system). It is, of course, conceivable that arteriosclerotic changes and cancers in general might both be related to a heightened metabolism finding outlets in various expressions of restless cellular activity, but it is not reasonably conceivable that this relationship would so strikingly involve cancers of the bronchial mucosa and not those of tissues without direct exposure to airborne irritants or carcinogens.

In adding this facet to our Cincinnati survey, we considered it wise to exclude from consideration cancers of the digestive and excretory systems and to limit ourselves entirely to primary malignant tumors of the pancreas, prostate, central nervous system and bones (#157, 177, 193, and 196, International List of Causes of Death). Cincinnati resident deaths from these causes for 4 years (1952–1955) were listed and survey contact obtained for 26 white males aged 50 to 59 and for 28 aged 60 to 69. The percentage of these falling into the various smoking categories are summarized below and compared with analagous percentages for the combined Cincinnati basin and suburban living populations and lung cancer deaths:

| *Surveyed Population* | *Age* | *Nonsmokers* % | *Pipe & Cigars* % | *Cigarettes* % |
|---|---|---|---|---|
| Living, white males | 50–9 | 22.7 | 12.7 | 64.6 |
| Cancer deaths (pancreas, etc.) | " | 23.7 | 7.7 | 69.2 |
| Lung cancer deaths | " | 3.2 | 6.4 | 90.4 |
| Living, white males | 60–9 | 31.9 | 17.9 | 50.2 |
| Cancer deaths (pancreas, etc.) | " | 25.0 | 28.6 | 46.4 |
| Lung cancer deaths | " | 8.6 | 7.9 | 86.5 |

(See addendum)

Men dying of these special types of cancer (pancreas, prostate, bones and nervous system) exhibit smoking habits essentially similar to those of the living-population controls, in sharp contrast to the much higher cigarette-smoking percentages of those dying from lung cancer. We, therefore, cannot entertain further the hypothesis of an underlying cellular restlessness as possibly responsible for all the observed phenomena. This strengthens the likelihood of real significance residing in the observed relationships. Tobacco smoking would thus seem significantly related to the development of lung cancer and cardiovascular disease, and

this tobacco smoking-disease relationship is further heightened for those with high motor driving mileages, and still further for those residing in the city's crowded basin districts. Here would seem to be appearing signs of urban man's tolerance limits if he is to survive as a smoker enmeshed in today's increasing motor-transport density.

To quote from our earlier article[2]: "Almost every tobacco novice is familiar with the acute effects of nicotine poisoning, the nausea, vomiting, clammy perspiration and prostration to a varying degree. Although amusing to the onlooker, these symptoms of ganglionic cell poisoning mean intense misery for the victim. Few people realize, however, that this passing discomfort from absorbed nicotine might often be only a feeble forerunner of more profound and fatal effects down through the years of tobacco usage. Nicotine is a powerful drug, with a characteristic action (stimulative-irritative-paralytic) on ganglion cells of the nervous system, particularly those of the involuntary or autonomic nervous system. Its action is indeed so characteristic that all other drugs exerting a similar effect are said to have a 'nicotinic' action.

"Some years ago Raymond Pearl[7] found the life span to be significantly shorter for smokers than for nonsmokers, without limiting the effect to any one cause of death. Now we begin to see the disease groupings in which tobacco smoking may be an important factor. In the air passages themselves, tobacco smoke irritation is significantly associated with the same three killing respiratory diseases already linked so closely with outdoor air pollution (Mills and Porter[3]). The excessively high rates for these diseases among men of dirty urban areas may well be due to a pyramiding of effects of the two forms of air pollution.

"It is well recognized that only tobacco smokers are afflicted with thromboangiitis obliterans, which causes so much trouble by cutting off circulation to the extremities, and that no treatment will be successful unless the habit is given up completely. Wise physicians also have become increasingly suspicious of nicotine's baneful influence in the rise of heart and vessel diseases to first rank among the causes of death in man. Certainly the statistics here set forth will in no way allay these suspicions. The association is equally close between smoking and peptic ulcer[2] or respiratory tract cancers[6]."

**Summary and Conclusions:** A direct association well beyond the realm of reasonable chance occurrence has been found to exist between cardiovascular disease death rates in white men and the amount of cigarette smoking in which they habitually indulge. Superimposed upon all categories of this cigarette smoking relationship is a further sharp death-rate rise associated with annual driving mileages above 12,000 miles, and still further superimposition in all categories is associated with residence in the solidly built-up basin areas of the city (Cincinnati).

These relationships are essentially analogous to those we found to exist for lung cancer death rates in white men, although the apparent exacerbating relationship was much greater between smoking and lung cancer deaths than between smoking and cardiovascular disease deaths.

ADDENDUM: Application of chi-square tests to the observed frequencies indicated no significant differences between the smoking habits of the special-type cancer victims and the living populations, but it showed a sharply significant difference between the lung cancer victims and those succumbing to the special-type cancers having no polluted air contact.

| | *Nonsmokers* | *Cigarette Smokers* | *Totals* |
|---|---|---|---|
| Living | 117 | 275 | 392 |
| Cancer deaths (pancreas, etc.) | 13 | 31 | 44 |
| Totals | 130 | 306 | 436 |
| $X^2 = .001$ (d.f. = 1) P .98 | | | |
| Cancer of lungs | 16 | 230 | 246 |
| Cancer of pancreas, etc. | 13 | 31 | 44 |
| Totals | 29 | 261 | 290 |
| $X^2 = 22.081$ (d.f. = 1) $P<.001$ | | | |

| | *Nonsmokers* | *Pipe & Cigar* | *Cigarettes* | *Total* |
|---|---|---|---|---|
| Living | 117 | 69 | 275 | 461 |
| Cancer (pancreas, etc.) | 13 | 10 | 31 | 54 |
| Totals | 130 | 79 | 306 | 515 |
| $X^2 = .461$ (d.f. = 2) $P<.5$ | | | | |
| Cancer (lungs) | 16 | 19 | 230 | 265 |
| Cancer (pancreas, etc.) | 13 | 10 | 31 | 54 |
| Totals | 29 | 29 | 261 | 319 |
| $X^2 = 24.510$ (d.f. = 2) $P<.001$ | | | | |

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## SUMMARIO IN INTERLINGUA

### Le Stress de Fumar Tabaco e de Conducer un Automobile in Relation a Mortes ab Causas Cardiac e Vascular


Ha essite constatate un association directe, ben in ultra del limites de un plausibile explication como occurrentia accidental, inter le mortalitate ab morbos cardiovascular in homines blanc e le grado de lor consumption habitual de cigarrettas. Superimponite a iste association in omne categorias es un acute augmento additional del mortalitate como function del conducer un automobile a totales annual de plus que 12.000 millias. A parte isto il ha ancora in omne categorias un superimponite association con domiciliation in le densemente urbanisate bassino alluvial del citate de Cincinnati.

Iste relationes es essentialmente analoge al relationes constatate per nos pro le mortalitate ab cancere pulmonar in homines blanc, ben que le apparente effecto exacerbante de fumar super le mortalitate ab cancere pulmonar esseva multo plus grande que illo de fumar super le mortalitate ab morbos cardiovascular.

# SERUM GAMMA GLOBULIN LEVELS IN CHRONIC LYMPHOCYTIC LEUKEMIA*

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The association of agammaglobulinemia and chronic lymphocytic leukemia in 3 patients has been previously reported (Brem and Morton[2] and Jim and Reinhard[7]).† Of vital importance is the frequency with which this association occurs in these individuals. In this report the serum gamma globulin levels as determined by serum electrophoresis are presented in a series of 50 unselected patients with chronic lymphocytic leukemia.

**Materials and Methods.** The sera from 50 unselected patients with chronic lymphocytic leukemia were studied. All patients, mostly whites and a few Negroes, were adults of both sexes. They were in various stages of their disease processes and were receiving either no therapy or being actively treated at the time of study with a variety of antileukemic agents. The serum proteins were analyzed by the technique of filter paper electrophoresis. Twenty cubic millimeters of each serum were applied as 2 cm. bands on Whatman 3 MM filter paper. The paper was then supported between two siliconized glass plates, allowed to equilibrate 30 minutes and the separation accomplished with Veronal buffer (pH 8.6, ionic concentration 0.1) at 320 volts, 15 to 20 milliamperes, for 8 hours at room temperature. The paper was then dried immediately and stained with 1% bromphenol blue dye. Quantitation of the protein fractions was accomplished with a Spinco Analytrol scanner.

**Results.** The results of paper electrophoresis of the serum proteins in 50 patients with chronic lymphocytic leukemia are tabulated in Table 1. The serum gamma globulins ranged from apparent complete absence to moderate increases in concentration. There was complete absence of gamma globulin in one serum.‡ Lesser degrees of hypogammaglobulinemia were found in approximately 34% of the cases studied while hypergammaglobulinemia was encountered in the remaining 24%. No consistent changes were found in the albumin, alpha or beta globulins except a tendency for the albumin to fall and the alpha and beta globulins to rise. No abnormal globulins characterized by narrow, tall, sharp peaks were seen on electrophoresis.

**Discussion.** A wide range of serum gamma globulin concentration may be found in chronic lymphocytic leukemia. The serum gamma globulin may be apparently absent, or its concentration may be diminished, normal or increased. Agammaglobulinemia or extreme hypogammaglobulinemia, however, appears to be a rare occurrence while slight to moderate degrees of hypogammaglobulinemia are encountered more frequently.

The mechanism by which agammaglobulinemia develops in chronic lymphocytic leukemia is not known. Destruction or replacement of the reticuloendothelial, lymphatic or plas-

*This work was completed during the tenure of a U.S. Public Health Service Postdoctoral Research Fellowship at the Department of Medicine, Washington University School of Medicine, St. Louis, Mo.

†A fourth patient is under the observation of Dr. M. M. Wintrobe at the present time[15].

‡A short clinical case report of this patient has been published elsewhere[7].

TABLE 1.—SERUM PROTEIN ELECTROPHORETIC FINDINGS IN 50 PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

| | *Relative Percentage* | | | | |
|---|---|---|---|---|---|
| | *Globulins* | | | | |
| *Case No.* | *Gamma* | *Beta* | *Alpha 2* | *Alpha 1* | *Albumin* |
| 1* | 0 | 17.0 | 18.0 | 9.7 | 56.0 |
| 2 | 2.9 | 7.3 | 7.9 | 2.8 | 79.0 |
| 3 | 4.8 | 15.1 | 7.4 | 3.3 | 69.3 |
| 4 | 5.7 | 13.7 | 12.2 | 10.8 | 57.5 |
| 5 | 5.8 | 15.9 | 12.4 | 8.5 | 57.4 |
| 6 | 5.9 | 11.7 | 13.1 | 7.2 | 62.0 |
| 7 | 6.3 | 20.2 | 7.2 | 4.5 | 61.7 |
| 8 | 7.9 | 8.7 | 1.6 | 1.6 | 80.1 |
| 9 | 8.5 | 8.0 | 11.3 | 5.7 | 66.4 |
| 10 | 8.9 | 15.3 | 6.4 | 5.3 | 64.0 |
| 11 | 8.9 | 8.9 | 13.1 | 7.7 | 61.3 |
| 12 | 9.0 | 12.2 | 6.8 | 3.4 | 68.6 |
| 13 | 9.6 | 10.7 | 13.9 | 5.3 | 60.5 |
| 14 | 10.5 | 11.7 | 11.3 | 2.7 | 63.8 |
| 15 | 10.7 | 12.8 | 6.7 | 4.7 | 65.0 |
| 16 | 11.0 | 19.3 | 17.7 | 8.8 | 43.2 |
| 17 | 11.3 | 11.6 | 8.4 | 4.7 | 64.0 |
| 18 | 12.1 | 14.5 | 7.9 | 5.4 | 60.0 |
| 19 | 12.6 | 6.6 | 2.0 | 0.6 | 78.1 |
| 20 | 13.4 | 20.1 | 19.0 | 5.2 | 42.2 |
| 21 | 13.6 | 15.3 | 6.3 | 2.4 | 62.3 |
| 22 | 13.9 | 12.4 | 6.9 | 2.7 | 64.0 |
| 23 | 14.1 | 13.9 | 11.2 | 6.5 | 54.3 |
| 24 | 14.2 | 14.2 | 13.0 | 4.5 | 54.0 |
| 25 | 14.6 | 23.9 | 19.0 | 5.3 | 36.7 |
| 26 | 15.6 | 8.9 | 6.1 | 3.3 | 66.0 |
| 27 | 16.5 | 15.9 | 12.7 | 3.4 | 51.4 |
| 28 | 17.1 | 8.7 | 9.8 | 2.8 | 61.6 |
| 29 | 17.2 | 19.1 | 8.4 | 5.1 | 50.1 |
| 30 | 17.2 | 12.2 | 8.1 | 2.8 | 59.6 |
| 31 | 17.6 | 16.3 | 10.0 | 1.6 | 54.5 |
| 32 | 18.5 | 12.2 | 18.4 | 3.8 | 47.0 |
| 33 | 18.6 | 14.7 | 15.7 | 8.5 | 42.4 |
| 34 | 19.1 | 8.2 | 4.3 | 5.0 | 63.3 |
| 35 | 20.3 | 19.9 | 12.6 | 5.7 | 41.4 |
| 36 | 20.5 | 8.7 | 14.9 | 3.6 | 52.3 |
| 37 | 21.8 | 19.3 | 15.1 | 9.4 | 34.4 |
| 38 | 23.1 | 10.7 | 9.3 | 3.9 | 53.0 |
| 39 | 24.0 | 12.0 | 12.6 | 8.2 | 43.2 |
| 40 | 24.3 | 9.2 | 4.6 | 0.5 | 61.3 |
| 41 | 24.4 | 16.7 | 15.0 | 6.5 | 37.4 |
| 42 | 25.7 | 8.6 | 6.7 | 4.6 | 54.3 |
| 43 | 26.6 | 14.2 | 10.9 | 5.2 | 43.0 |
| 44 | 27.7 | 13.2 | 16.6 | 6.7 | 35.8 |
| 45 | 27.8 | 12.4 | 8.9 | 4.6 | 46.2 |
| 46 | 28.0 | 8.9 | 11.1 | 1.8 | 50.2 |
| 47 | 32.6 | 11.8 | 10.3 | 4.1 | 31.2 |
| 48 | 34.4 | 16.8 | 8.0 | 6.4 | 34.4 |
| 49 | 35.2 | 7.8 | 5.2 | 4.7 | 47.0 |
| 50 | 48.9 | 6.5 | 4.4 | 1.0 | 39.1 |
| Ave. 15 normal adults | 17.3 | 11.3 | 6.6 | 3.6 | 61.1 |

*Tiselius determination.

ma cell systems by the leukemic process could conceivably lead to impaired production of gamma globulin. In other diseases related to chronic lymphocytic leukemia, such as reticulum cell sarcoma (Wall[14]), lymphosarcoma (Wall[14]), "malignant lymphoma" (Arends, Coonrad and Rundles[1]) Hodgkin's disease (Jim[6]) giant follicular lymphoma (Jim[6]) and in benign thymomas (Good and Zak[5], and Ramos and Loeb[11]), complete or almost complete absence of serum gamma globulin may be found. However, this is not the final explanation as agammaglobulinemia is rare in other types of acute or chronic leukemia. Thus far only one patient with chronic granulocytic leukemia has been reported with agammaglobulinemia (Capone, Rossi-Espagnet and Ruggeri[4]).

Except for a tendency towards hypoalbuminemia and rise in alpha and beta globulins, no diagnostic patterns were found on serum protein electrophoresis in the present series. In other published reports on the serum protein electrophoretic patterns in chronic lymphocytic leukemia, normal or similar nonspecific changes were found (Brown *et al.*[3], Neely and Neill[8], Nitshe and Cohen[9], Petermann *et al.*[10], Roboz *et al.*[12], Rundles *et al.*[13], and Wall[14].)

Determination of the gamma globulin concentration in chronic lymphocytic leukemia may be important when steroid therapy is contemplated for treatment for an associated severe hemolytic anemia. The lack of serum gamma globulin plus steroid therapy may result in increased susceptibility to infections in these individuals. Splenectomy or the combined parental administration of gamma globulin with steroids may be the choice of treatment for the hemolytic process in this situation.

**Summary.** The serum gamma globulin levels as determined by serum protein electrophoresis are reported in 50 unselected patients with chronic lymphocytic leukemia. The gamma globulin ranged from complete absence to moderately increased levels. Hypogammaglobulinemia was found in approximately one-third and hypergammaglobulinemia in one-fourth of the patients studied. Agammaglobulinemia was found in only a single patient. Except for a tendency towards hypoalbuminemia and elevation of the alpha and beta globulins, no consistent changes were found in the serum protein electrophoretic pattern in chronic lymphocytic leukemia.

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## SUMMARIO IN INTERLINGUA

### Nivellos Seral de Globulina Gamma in Chronic Leucemia Lymphocytic

Es reportate le nivellos seral de globulina gamma, determinate per electrophorese del proteinas del sero in 50 non-seligite patientes con chronic leucemia lymphocytic. Le nivellos del globulina gamma variava inter zero e valores moderatemente augmentate. Hypogammaglobulinemia esseva trovate in circa un tertio e hypergammaglobulinemia in circa un quarto del patientes studiate. Agammaglobulinemia esseva restringite a un sol patiente. A parte le tendentia hypoalbuminemic e le elevation de globulina alpha e globulina beta, nulle uniforme alterationes esseva constatate in le configuration electrophoretic del proteinas seral de patientes con chronic leucemia lymphocytic.

## SUMMARIO IN INTERLINGUA

*(See page 48 for original article)*

### Studios Hemodynamic in Patientes con Cirrhosis de Laennec

1. Cirrhosis de Laennec es accompaniate (39 pro cento) o non accompaniate (61 pro cento) de un augmento in le rendimento cardiac.

2. Un augmento del volumine plasmatic es trovate in 72 pro cento del casos. Illo es trovate in 100 pro cento del casos con augmento del indice cardiac.

3. Augmentos del cuneate pression hepato-venose es trovate in 100 pro cento del casos.

4. Le resistentia systemic es reducite in 72 pro cento del casos de cirrhosis de Laennec.

5. Augmentos del differentia arterio-venose de oxygeno non esseva apparente in le presente serie.

6. Un allargate pression de pulso esseva constatate, de accordo con previe observationes (Cournand *et al.*).

7. Le augmento del rendimento cardiac in casos de cirrhosis de Laennec es probabilemente le effecto de un reduction del resistentia systemic e etiam de derivation arterio-venose in le extremitates, con augmento del retorno venose. Isto es de accordo con Silverstein. Le secunde del duo factores merita studios additional.

8. Catheterisation hepato-venose con determinationes de pression cuneate es un methodo logic e plausibile pro studios preparatori in patientes considerate pro chirurgia derivational.

# HEMODYNAMIC STUDIES IN PATIENTS WITH LAENNEC'S CIRRHOSIS*

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The resting cardiac output in patients with Laennec's cirrhosis of the liver has been reported as elevated (Kowalski and Abelman[19], and Taylor and Myers[34]). Factors which have been considered as producing an elevation in the cardiac output in cirrhosis are: 1) a lowering of the systemic resistance, 2) an increase in plasma volume (Bateman *et al.*[1], Eisenberg[10], Hiller *et al.*[15], Hyde *et al.*[16] and Perera[28]), and 3) an arteriovenous fistula effect due to the multiple arteriovenous shunts in parallel within the cirrhotic liver (Dock[8], Herrick[14] and Prinzmetal *et al.*[30]).

In view of the fact that the above-mentioned observations were made in different groups of patients, it seemed desirable to determine the relative frequency of these alterations in one group of patients so that their interrelations could be elucidated.

**Methods.** Eighteen patients (14 males and 4 females) with cirrhosis of the liver were selected. With the exception of one subject, all were admitted alcoholics and all gave a definite history of dietary deficiency. Their ages varied from 31 to 64 years for the males, the females being 34, 38, 47 and 50 years respectively. After a thorough workup which included the history, physical examination, roentgenographic studies of the upper gastrointestinal tract and esophagus and appropriate biochemical studies, hepatic catheterization was carried out. All of the patients were free of cardiac pathology and their electrocardiograms were normal (one patient had a grade II systolic murmur at the apex but fluoroscopic studies were negative). Each patient, except one, had a positive needle biopsy of the liver substantiating the clinical diagnosis of Laennec's cirrhosis.

Pressures and blood samples for oxygen content were taken in the hepatic vein, wedged and "free," from the cardiac chambers and pulmonary vessels. All pressures were recorded by way of a Statham Strain Gauge on a Sanborn Polyviso Recorder in millimeters of mercury. The mean systemic blood pressure was recorded from the femoral artery by electrical integration. Systemic resistance was calculated from the mean systemic pressure and cardiac output.

After the catheter was in the main pulmonary artery the cardiac output was measured using the direct Fick method. Expired air was collected, after two 5-minute washing periods in a Collins Chain-Compensated Gasometer and its oxygen content was measured with a Beckman Model C Oxygen Analyzer. Simultaneous blood samples were drawn from the main pulmonary artery and

*This study was supported in part by the Kansas Heart Association.
†Public Health Service Research Fellow, National Institute of Arthritis and Metabolic Diseases.

the femoral artery during the collection period. All blood samples were analyzed according to the method of Van Slyke and Neill.

Blood volume studies were done with 25 mg. of Evans blue dye (T–1824)* following the modification in technique by Gregerson[13]. A few blood volumes were done on the wards prior to catheterization. The remainder were done via the catheter which had been placed in the right subclavian vein. Ten cubic centimeter aliquots of blood were drawn prior to giving the dye and at 10-, 20- and 30-minute intervals after its administration. The dye concentrations were extrapolated to injection time.

Serum glutamic oxalacetic transaminase, serum iron and blood ammonia values were measured from hepatic vein samples. These will be discussed in a future article being prepared.

In addition to the 18 patients with liver cirrhosis, the hepatic wedged pressure was ascertained in 17 patients free of liver disease.

CARDIAC INDEX. A normal cardiac index was considered to be 3.45 L./min./M² with an average standard deviation of ± .662 L./min./M². These figures were calculated from five series of normal patients reported in the literature (Chapman *et al.*[4], Cournand *et al.*[6], Dexter *et al.*[7], Ebert *et al.*[9] and Silverstein[32]) using the Fick method.

In this study 7 patients (39%) were found to have an increase in cardiac index above the normal range (4 L./min./M²), 7 were normal and 4 were below normal (Table 1).

TABLE 1.—PERTINENT DATA EXTRACTED FROM TABLES 2 AND 3 FOR EASIER COMPARISON

| *Name* | *Hepatic Vein Wedge (mm. Hg)* | *Cardiac Index (L./min./M²)* | *Systemic Resistance (Dynes Sec. cm⁻⁵/M²)* | *Plasma Volume (ml./Kg.)* | *Total Blood Vol. (ml./Kg.)* |
|---|---|---|---|---|---|
| C.E. | 18.5 | 4.3 ↑ | 596 ↓ | 60 ↑ | 111 ↑ |
| J.F. | 9.5 | 4.3 ↑ | 741 ↓ | 79 ↑ | 123 ↑ |
| E.Y. | 20.0 | 4.3 ↑ | 484 ↓ | 56 ↑ | 87 N |
| P.T. | 18.0 | 2.8 | 886 ↓ | 60 ↑ | 93 ↑ |
| J.L. | 13.0 | 4.0 | 498 ↓ | 59 ↑ | 92 ↑ |
| J.P. | 13.0 | 3.1 | 537 ↓ | 30 ↓ | 52 ↓ |
| H.A. | 10.0 | 3.4 | 619 ↓ | 57 ↑ | 102 ↑ |
| C.K. | 11.0 | 2.8 | 975 ↑ | 40 ↓ | 75 N |
| O.B. | 10.5 | 1.8 ↓ | 1518 ↑ | 52 ↑ | 72 N |
| F.H. | 22.0 | 4.8 ↑ | 411 ↓ | 61 ↑ | 88 N |
| V.W. | 36.0 | 5.9 ↑ | 488 ↓ | 79 ↑ | 100 ↑ |
| E.W. | 10.0 | 1.1 ↓ | 2528 ↑ | 48 N | 84 N |
| J.O. | | 4.7 ↑ | 497 ↓ | 67 ↑ | 105 ↑ |
| W.C. | | 2.8 | 774 ↓ | 49 ↑ | 90 ↑ |
| H.C. | | 1.1 ↓ | 1880 ↑ | 52 ↑ | 67 ↓ |
| S.L. | | 2.2 ↓ | 1087 ↑ | 33 ↓ | 58 ↓ |
| C.T. | 9.0 | 3.8 | 555 ↓ | 40 ↓ | 60 ↓ |
| S.R. | 11.0 | 4.6 | 625 ↓ | 59 ↓ | 83 N |

PLASMA VOLUME. An increase in plasma volume was found in thirteen (72%) of the 18 patients, only one being normal and 4 less than normal (Table 1). All of the patients with an increase in cardiac index, except one (C.T.), had an increase in plasma volume. An increased plasma volume was found in 4 of the patients with a normal cardiac index and 2 patients with a reduced cardiac index had an increase in plasma volume.

Plotting revealed a definite correlation between the cardiac index and

*The Evans blue dye was a gift of Eli Lilly and Company.

plasma volume (correlation coefficient .77) (Fig. 1).

SYSTEMIC RESISTANCE-BLOOD PRESSURE. The systemic resistance was reduced in 13 of the patients with Laennec's cirrhosis (72%) whereas it was increased in 5 patients. The resistance was reduced in all of the patients with increased and normal cardiac indices, except one (C.K.). The highest values of systemic resistance were found in the patients with a reduced cardiac index.

All of the patients with a reduced systemic resistance had an increased plasma volume except J.J. and C.T., including one which had a systemic resistance of 1880 dynes seconds centimeters$^{-5}$ and an increase in plasma volume.

Plotting revealed a definite correlation between the cardiac index and the

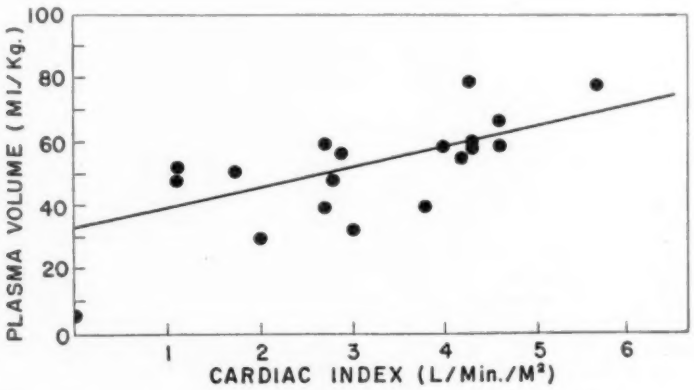


Fig. 1.—Plotting the cardiac index against the plasma volume reveals a definite correlation (correlation coefficient = .77, $p<.01$).

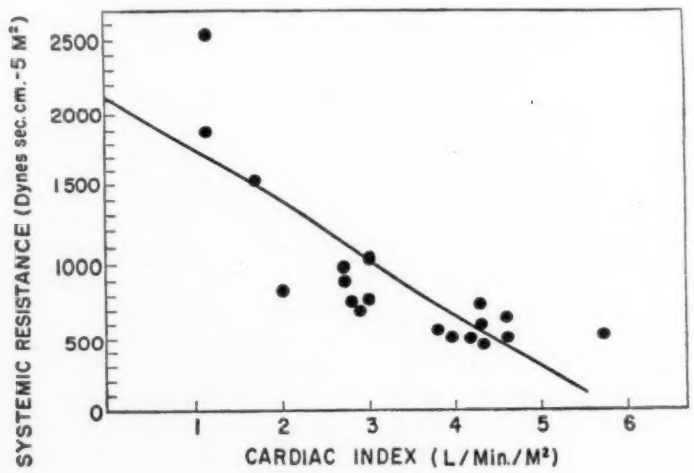


Fig. 2.—Plotting the cardiac index against the systemic resistance reveals a definite correlation (correlation coefficient = .68, $p<.01$).

TABLE 2.—DATA OBTAINED DURING CATHETERIZATION INCLUDING OXYGEN CONTENT, CAPACITY AND MEASURED A–V OXYGEN DIFFERENCE

| | Oxygen Capacity (Vol. %) | Hepatic Wedge Pressure (mm. Hg) | Oxygen-Wedge Sample | | "Free" Hepatic Vein Pressure (mm. Hg) | Oxygen-"Free" Sample | | Oxygen-Peripheral Arterial Sample | | A–V Oxygen Difference (Peripheral Artery-Hepatic Vein) (Vol. %) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Content (Vol. %) | Saturation (%) | | Content (Vol. %) | Saturation (%) | Content | Saturation | |
| W.C. | 18.0 | | | | | | | 15.7 | 88.9 | |
| J.O. | 14.7 | | | | | | | 13.6 | 95.4 | |
| C.E. | 14.6 | 18.0 | 9.2 | 64.8 | 4 | 10.9 | 77.0 | 12.6 | 88.4 | 3.4 |
| J.F. | 14.7 | 10.0 | 9.1 | 63.4 | 5 | 9.1 | 63.4 | 13.8 | 94.8 | 4.7 |
| E.Y. | 18.8 | 20.0 | | | 14 | 11.4 | 62.2 | 16.8 | 90.6 | 5.4 |
| P.T. | 20.6 | 18.0 | | | 4 | 15.0 | 74.6 | 18.9 | 93.5 | 3.9 |
| S.L. | 19.6 | | | | | | | 18.0 | 94.0 | |
| J.L. | 14.5 | 13.0 | | | 4 | 10.5 | 74.2 | 13.3 | 94.2 | 2.8 |
| J.P. | 20.6 | 13.0 | 10.9 | 53.1 | 5 | | | 17.9 | 86.5 | 7.0 |
| H.A. | 20.8 | 10.0 | 12.9 | 68.2 | 3 | | | 19.4 | 91.3 | 6.5 |
| C.K. | 21.6 | 11.0 | 15.7 | 73.4 | 8 | | | 19.4 | 91.3 | 3.7 |
| O.B. | 16.1 | 10.5 | | | 5 | 10.6 | 67.6 | 14.7 | 92.8 | 4.1 |
| F.H. | 14.7 | 22.0 | 10.4 | 72.3 | 14 | | | 13.7 | 95.7 | 3.3 |
| H.C. | 11.0 | | | | | | | 10.8 | 100.0 | |
| V.W. | 10.2 | 36.0 | | | 11 | 8.1 | 82.4 | 9.2 | 93.8 | 1.1 |
| E.W. | 17.7 | 10.0 | 11.6 | 67.1 | 2 | | | 16.2 | 93.3 | |
| C.T. | 16.74 | 9.0 | | | 3 | 13 | 79.4 | 15.4 | 93.4 | 2.39 |
| S.R. | 12.91 | 11.0 | 9.90 | 77.7 | | | | 12.07 | 94.1 | 2.84 |

TABLE 3.—BLOOD VOLUME STUDIES, CARDIAC INDEX AND SYSTEMIC RESISTANCE MEASUREMENTS PERFORMED SUBSEQUENT TO CATHETERIZATION

| | Heart Rate (Per Min.) | Cardiac Index (L./M²) | Systemic Resistance per M² (Dynes Sec. cm⁻⁵) | Mean Blood Pressure (mm. Hg) | Pulse Pressure (mm. Hg) | Total Blood Volume (ml. kg.) | Plasma Volume (ml. kg.) | Total Red Cell Volume (ml. kg.) | Venous Pressure (cm N.S.S.) |
|---|---|---|---|---|---|---|---|---|---|
| W.C. | 84 | 2.8 | 774 | 100 | 75 | 90 | 49 | 41 | 9.5 |
| J.O. | 80 | 4.7 | 497 | 90 | 60 | 105 | 67 | 37 | |
| C.E. | 68 | 4.3 | 596 | 88 | 82 | 111 | 60 | 50 | 7.5 |
| J.F. | 100 | 4.3 | 741 | 85 | 40 | 123 | 79 | 44 | 13 |
| E.Y. | 100 | 4.3 | 484 | 75 | 45 | 87 | 56 | 31 | 6.5 |
| P.T. | 100 | 2.8 | 886 | 115 | 87 | 93 | 60 | 33 | |
| S.L. | 100 | 2.2 | 1087 | 102 | 64 | 58 | 33 | 25 | 16 |
| J.L. | 100 | 4.0 | 498 | 80 | 60 | 92 | 59 | 33 | 18 |
| J.P. | 100 | 3.1 | 537 | 93 | 60 | 52 | 30 | 22 | |
| H.A. | 100 | 3.4 | 619 | 92 | 53 | 102 | 57 | 45 | 10.5 |
| C.K. | 75 | 2.8 | 975 | 110 | 80 | 75 | 40 | 35 | 12 |
| O.B. | 100 | 1.8 | 1518 | 112 | 92 | 72 | 52 | 20 | 19 |
| F.H. | 140 | 4.8 | 411 | 85 | 60 | 88 | 61 | 27 | 11.3 |
| H.C. | 80 | 1.1 | 1880 | 97 | 101 | 67 | 52 | 14 | 8.5 |
| V.W. | 100 | 5.9 | 488 | 78 | 70 | 100 | 79 | 21 | |
| E.W. | 75 | 1.1 | 2528 | 90 | 60 | 84 | 48 | 36 | |
| C.T. | 75 | 1.1 | 555 | 80 | 68 | 60 | 40 | 20 | 13 |
| S.R. | 85 | 4.6 | 625 | 90 | 66 | 83 | 59 | 23 | 10.4 |

systemic resistance (correlation coefficient .68) (Fig. 2).

The systemic blood pressure in this series had a mean of 93 mm. Hg with a standard deviation of ± 12 mm. Hg. The pulse pressure had a mean of 68 mm. Hg with a standard deviation of ± 16 mm. Hg (Table 3).

Four of the patients had a systolic reading over 150 mm. Hg. Three of them had a diastolic pressure over 90 mm. Hg and one was 100 mm. Hg.

Venous pressures were obtained in 13 patients. They varied from 6.5 to 19 cm. of normal saline solution with a mean of 12 cm. of normal saline solution with a standard deviation of ± 4.2 cm. of normal saline solution.

HEPATIC VEIN WEDGE PRESSURE AND OXYGEN SATURATION. The hepatic wedge mean pressure in the series of normal patients was 6 mm. Hg with a standard deviation of ± 1 mm. Hg.

Fourteen of the 18 patients had hepatic catheterizations done with wedge pressure values from 9 to 36 mm. Hg, a mean of 16 mm. Hg and a standard deviation of ± 7 mm. Hg.

"Free" hepatic vein pressure had a mean of 6 mm. Hg and a standard deviation of ± 4 mm. Hg. The average increase in mean wedge pressures over "free" hepatic vein mean pressure was 9 mm. Hg.

Six of the patients with an increase in mean wedge pressure had an increase in cardiac index (33%), 6 had normal cardiac indices whereas the remaining 2 had reduced cardiac indices. Ten of the patients with an increase in wedge pressure had an increase in plasma volume (71%). Also, 11 of the 14 patients had a reduced systemic resistance (78%).

Oxygen content of the blood from the hepatic vein wedge was measured in 8 patients (Table 2). The values varied from 9.1 to 15.7 vol. % with a mean of 11.4 vol. % and a standard deviation of ± 2 vol. %. The difference between the oxygen content of wedge and "free" samples was 0.7 vol. %.

The arteriovenous difference between the mean arterial content and the mean oxygen content of the hepatic vein wedge samples was 3.8 vol. %.

**Discussion.** An increased resistance to the flow of blood through the liver is found in Laennec's cirrhosis. This has been well demonstrated by an increased venous pressure in the wedged hepatic venule by an occluding catheter tip (Stead *et al.*[33]). Increase in wedge pressure may be due to the obliteration of normally existing channels between the sinusoids and the hepatic vein. It may be due to transmission of hepatic arterial pressure through anastomoses, or due to hypoxia.

The normal wedged hepatic venous pressure measures between 4 and 6 mm. Hg (Myers[25] and Paton *et al.*[27]) (5.7 mm. Hg in our series of 17 patients without liver disease). Cirrhosis of the liver is pathologically characterized by simultaneously destructive as well as regenerative processes (Kelty *et al.*[17]). This reduces the number of sinusoidal pathways and normally found arteriovenous communications (Popper *et al.*[29] and Prinzmetal *et al.*[30]), increases the obstruction to blood flow, and pooling occurs in the portal circulation. With increase in blood volume and pressure in the portal vessels, collateral channels develop to handle the increasing load. That these are at best inadequate is expressed in the finding of an elevated wedge pressure by way of the catheter tip.

It has been suggested (Kretz[21] and McIndoe[23]) that arterial pressure is transmitted to the sinusoid by existence of direct anastomoses between the hepatic artery, portal vein and the sinusoids. These have been demonstrated in the normal liver (Herrick[14], Popper *et al.*[29] and Prinzmetal *et al.*[30]),

and surgeons doing shunt procedures, have reported dilated and tortuous hepatic arteries. These suggest an increased arterial flow to the liver (Myers[26]), and complicate explanation of portal hypertension.

Logically the site of the obstruction to portal flow is in the liver itself. Direct measurement of wedge pressure before and after a shunting procedure, reveals little reduction in the pressure (Morton and Whelan[24]).

An increase in total blood volume was measured in 44% of the cases (8) in this series. This was accompanied by an increase in plasma volume in all cases except one. Such would suggest that increase in total blood volume is primarily due to an increase in plasma volume.

Increases in plasma volume in cirrhosis may be due to several factors. Anemia, ascitic accumulation, altered steroid metabolism and increased salt retention have been suggested.

Anemia below 7.5 gm. of hemoglobin per 100 ml. is accompanied by an increase in plasma volume (Brannon *et al.*[3], Chodos *et al.*[5] and Gibson *et al.*[12]). Only one case in this series (V.W.) had an anemia of this magnitude and it likely contributed to her increase in plasma volume.

Ascitic accumulation, by increasing the surface area of the body, to which plasma volume is directly related, reportedly will increase total blood volume (Bradley *et al.*[2]). Moderate to marked ascites was present in 2 cases (W.C. and J.O.).

Estrogen, circulating in excess, is believed to cause salt retention (Lloyd and Williams[22] and Robinson and Farr[31]), as well as peripheral vasodilatation. Any increase in the sodium ion concentration probably affects the osmoreceptor centers which in turn stimulate the posterior pituitary to secrete antidiuretic hormone. This substance acting on the distal renal tubules could cause retention of water to dilute sodium ions to proper concentration for electrolytic balance. Aldosterone has also been suggested as a factor in sodium retention in cirrhosis of the liver (Myers[26]). In our cases excretion of sodium in the urine was at a low level indicating its maximum retention. Such has often been observed (Farnsworth[11]). An increase in blood volume is the end result.

Reduction in systemic resistance in cirrhosis may be due to several factors, namely vasodilatation and increase in blood volume. Several physical signs evidence peripheral vasodilatation such as warm, sweaty palms, cutaneous vascular spiders, and warm extremities. It has been suggested that these are indirectly the result of an excess of circulating estrogen.

Raising the body temperature above normal is accompanied by peripheral vasodilatation and a fall in systemic resistance. Each patient in this series had daily temperatures of 1.5 to 2° F. above normal, a common observation in cirrhosis of the liver.

In addition, a widened pulse pressure was measured (68 mm. Hg with a standard deviation of $\pm$ 16 mm. Hg), another evidence of peripheral vasodilatation. Since normal systolic blood pressures were maintained in most of the cases in the series, the widened pulse pressure occurred at the expense of the diastolic pressure. In other words, the systemic resistance was reduced.

Increases of total blood volume are accommodated by greater stretching of elastic vascular walls. A reduction in systemic resistance due to decreasing the total amount of vascular frictional surface follows.

This brings us to consideration of cardiac output in cirrhosis of the liver. An increase in cardiac output has been

reported previously (Kowalski and Abelman[19] and Taylor and Myers[34]) and is confirmed in this series. Why is the output increased? It could be related to an increase in heart rate (Kowalski and Abelman[19]), an increase in plasma volume, a decrease in systemic resistance, or any combination of these three.

Three-fourths of the cases in this group had an increase in blood volume and an increase in stroke volume. The average resting heart rate in this series was 93 beats per minute. This is above normal.

Reduction in systemic resistance does contribute to increased cardiac output through an increased heart rate reflexly set about by reduction of blood pressure.

As the plasma volume increases, the cardiac output, as verified by the cardiac index, gradually increases. Plotting the cardiac index against the plasma volume in this series reveals a high degree of correlation ($r = .77$) (Fig. 1).

Plotting the cardiac index against the systemic resistance also reveals a high degree of correlation ($r = .68$) (Fig. 2). From these observations an increase in cardiac output can be definitely related to an increase in plasma volume and a decrease in systemic resistance. From the data, it is not possible to say whether the plasma volume increases first (72% of the cases) or following the drop in systemic resistance (72% of the cases).

All cases catheterized had an increased wedged hepatic vein pressure whereas only 33% had an increase in cardiac index. It would appear that although an increase in hepatic vein pressure is characteristic of cirrhosis, relationship to increased cardiac output is not yet clear. It was originally hoped to relate increased cardiac output to vascular changes within the liver itself. This cannot be done with the information obtained.

**Summary.** (1) Laennec's cirrhosis may (39%) or may not (61%) be accompanied by an increase in cardiac output.

(2) An increase in plasma volume is found in 72% of the cases, but in 100% of the cases with an increased cardiac index.

(3) An increased wedged hepatic vein pressure is found in 100% of the cases.

(4) Systemic resistance is reduced in 72% of the cases of Laennec's cirrhosis.

(5) An increase in arteriovenous oxygen difference was not apparent in this series.

(6) A widened pulse pressure was found in this series confirming previous observations (Cournand *et al.*[6]).

(7) The increase in cardiac output in cases of Laennec's cirrhosis is probably due to a reduction in systemic resistance as well as arteriovenous shunting in the extremities with an increased venous return as suggested by Silverstein[32]. The latter feature is worth further study.

(8) Hepatic vein catheterization with wedge pressure determinations is a reasonable and logical method of preparatory study on patients being considered for shunt surgery.

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*(Interlingua on page 47)*

# THE CAUSE OF DEATH IN PATIENTS WITH LAENNEC'S CIRRHOSIS

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Laennec's cirrhosis is commonly encountered clinically and at necropsy. Yet information concerning the cause of death in such patients is not available in general texts of pathology and medicine. Current opinion on this subject in books on liver diseases (Bockus[3], Lichtman[12], Schiff[15] and Spellberg[16]) and the general literature is based on only a few reports of series of cases with no critical evaluation of such important factors as selection of patients, manner of classification, confirmation by necropsy examination, and the like. A review of the recent literature yields no article which summarizes the data on a large number of cases from different series of patients.

Such information is particularly important now to evaluate the effectiveness of therapeutic procedures (for example, portacaval shunts, balloon tamponade of the esophagus) which are presently in dispute. It is necessary in order to appreciate the effects of changing nutritional standards and for comparison with other geographical areas having different nutritional levels. Such information offers a basis for noting the results of chemotherapeutic agents in the control of pyogenic, tuberculous, and syphilitic infections in cirrhotic patients. The effectiveness of the current greater use of blood replacement may also be observed. Finally, such data are necessary in order to study and understand the natural history of cirrhosis of the liver. With the increased frequency of such cirrhosis-inducing diseases as infectious hepatitis, alcoholism, and nutritional deficiencies, this assumes additional importance.

These data evaluate other opinions concerning the cause of death in cirrhotic patients and offer an easily accessible summary of some previous reports. Totaling large numbers of cases dilutes errors in classification, arithmetic inconsistencies, temporal and geographical factors and other unrecognized variables in any individual series.

REVIEW OF THE LITERATURE. The reports which appear in Table 1 are summarized below in regard to time period, source of material, selection and evaluation of cases and confirmation by postmortem examination.

In 1931, Chapman, Snell, and Rowntree[4] reviewed 300 cases of portal cirrhosis from the Mayo Clinic. One hundred and twelve were selected because of the presence of ascites. Cases with complicating factors such as primary cardiac or renal disease,



TABLE 1.—CAUSE OF DEATH IN REPORTED SERIES OF PATIENTS WITH LAENNEC'S CIRRHOSIS

TABLE 1.—CAUSE OF DEATH IN REPORTED SERIES OF PATIENTS WITH LAENNEC'S CIRRHOSIS

| | | *Directly Due to Cirrhosis* | | | | | | | | *Not Directly Due to Cirrhosis* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Total Cases Died* | *Liver Failure* | | *Bleeding Esophageal Varices* | | *Primary Carcinoma Liver* | | *Thrombosis of Portal Vein* | | *Infection* | | *Tuberculosis* | | *Postoperative* | | *Others* | | *Source of Cases* |
| | | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | |
| Chapman, Snell & Rowntree[4] | 84 | 18 | 21 | 16 | 19 | | | | | 15 | 18 | | | 6 | 7 | 29 | 35 | Prior to 1931. Exact dates not given. Mayo Clinic |
| Henrikson[11] | 73 | 18 | 25 | 14 | 19 | | | 3 | 4 | 16 | 22 | | | 6 | 8 | 16 | 22 | 1916–1932. Minn. General & Univ. Minn. Gen. Hospitals |
| Ratnoff & Patek[14] | 244 | 77 | 32 | 55 | 22 | | | | | 42 | 17 | 4 | 2 | 39 | 16 | 27 | 11 | 1916–1938. Five private hospitals in N.Y.C. |
| Fagin & Thompson[8] | 29 | 15 | 52 | 8 | 27 | | | | | 4 | 14 | | | | | 2 | 7 | 1926–1943. U.S. Marine Hosp., Detroit |
| Patek *et al.*[13] | 30 | 12 | 40 | 7 | 24 | | | 1 | 3 | 4 | 13 | 1 | 3 | 1 | 3 | 4 | 13 | 10 years. Goldwater Memorial Hosp., N.Y. |
| Douglass & Snell[5] | 85 | 26 | 31 | 42 | 49 | | | | | 5 | 6 | | | | | 12 | 14 | 1940–1944. Mayo Clinic. |
| * Armas-Cruz *et al.*[1] | 76 | | | 13 | 17 | | | | | ? | ? | ? | ? | ? | | ? | | 4 years. Univ. of Chile Hosp. |
| Halstead & Fainer[10] | 58 | 16 | 28 | 27 | 46 | | | | | 3 | 5 | 1 | 2 | | | 11 | 19 | 1951–1952. Wadsworth V.A. Hospital, Los Angeles. |
| Blumenau[2] | 188 | 15 | 8 | 9 | 5 | | | | | 48 | 26 | 29 | 15 | | | 87 | 46 | 1909–1918. Frankfort, 12,761 necropsies. |
| † Eppinger[6] | 135 | 22 | 16 | 22 | 16 | | | | | 38 | 28 | 13 | 10 | | | 40 | 30 | 1905–1925. Vienna. |
| Evans & Gray[7] | 217 | 26 | 12 | 30 | 14 | | | 5 | 2 | 93 | 43 | 6 | 3 | | | 57 | 26 | 1918–1937. Los Angeles County Hospital, 17,874 necropsies. |
| Patek *et al.*[13] | 45 | 7 | 16 | 10 | 22 | | | 8 | 18 | 13 | 28 | | | | | 7 | 16 | 10 years. Goldwater Memorial Hosp., N.Y. |
| Halstead & Fainer[10] | 44 | 8 | 18 | 12 | 27 | 1 | 2 | | | 6 | 14 | 2 | 5 | 3 | 7 | 12 | 27 | 1949. Wadsworth V.A. Hospital, Los Angeles, 625 necropsies. |
| † Hall, Olsen & Davis[9] | 782 | 134 | 17 | 143 | 18 | 21 | 3 | | | 206 | 26 | 55 | 7 | | | 223 | 35 | 1933–1946. Los Angeles County Hospital, 16,600 necropsies. |
| Wallach, Hyman & Angrist | 300 | 50 | 17 | 63 | 21 | 13 | 4 | 5 | 3 | 60 | 20 | 10 | 3 | 13 | 4 | 86 | 28 | 1936–1950 Queens Gen. Hosp., N.Y., 8,676 necropsies. |
| TOTALS: | | | | | | | | | | | | | | | | | | |
| Clinical Series[1,4,5,8,10,11,13,14] | 603 | 182 | 30 | 169 | 28 | | | 4 | 1 | 89 | 15 | 6 | 1 | 52 | 8 | 101 | 17 | |
| Pathological Series[2,6,7,9,10,13] | 1711 | 262 | 15 | 289 | 17 | 35 | 2 | 18 | 1 | 464 | 27 | 115 | 7 | 16 | 1 | 512 | 30 | |
| All Series | 2314 | 444 | 19 | 458 | 20 | 35 | 2 | 22 | 1 | 553 | 24 | 121 | 5 | 68 | 3 | 613 | 26 | |

All per cent figures expressed as approximate whole numbers.

* Not included in totals. † Numbers are approximate calculated from figures expressed as per cent.

or chronic peritonitis, were excluded but a number of cases with associated "chronic splenic disease," chronic infection of the biliary tract, or visceral syphilis were included. Eighty-four of these patients died and only 28 were examined postmortem. The liver was examined at operation in an additional 28 patients but biopsy for histologic confirmation is not mentioned. Henrikson[11] summarized the cases of cirrhosis of the liver from the Minneapolis General Hospital and the University of Minnesota General Hospitals from 1916 to 1932. These were composed of 84 proven cases of cirrhosis, only 64 of which were portal, and 78 other cases of probable cirrhosis. Sixty-seven patients were studied at necropsy. Ratnoff and Patek[14] reviewed the case records from five private hospitals in New York City for varying periods between 1916 and 1938. They excluded 49 cases (11%) which were asymptomatic. The cause of death is given in 213 fatal cases but there is no note of how many came to necropsy. The number of cases listed totals to 244 rather than 213. In a subsequent report, Patek *et al.*[13] reviewed 160 patients with hepatic cirrhosis and studied 124 who were symptomatic. The principal causes of death are listed separately for 45 patients examined post mortem and for 30 patients in whom the diagnosis was presumptive. Fagin and Thompson[8] analyzed 71 cases of portal cirrhosis seen at the U.S. Marine Hospital in Detroit from 1926 to 1942. There were 29 deaths and 18 necropsies in this group. Cirrhosis was an incidental necropsy finding in 2 patients.

Douglass and Snell[5] selected 444 cases of Laennec's cirrhosis seen at the Mayo Clinic which were not complicated by the concomitant presence of other serious disease potentially capable of causing death. Cases with malignant tumors, diabetes, severe hypertension or cardiac disease, extreme obesity, tuberculosis and other chronic pulmonary diseases, and the like, were excluded. The data on the manner of death is based on 85 patients, only a few of whom died in Rochester Hospital. Thirty were examined post mortem; apparently, not all of these examinations were conducted at the Mayo Clinic. Armas-Cruz *et al.*[1] reported on 208 cases of portal cirrhosis from the University of Chile Hospital. They state: "Of 76 cirrhotic deaths, hemorrhage was the immediate cause in 13 (17.1%)." The frequency of death from other causes is not given and the number of necropsies is not noted.

Blumenau[2] tabulated the causes of death in patients with Laennec's cirrhosis during the period 1908 to 1918. These occurred among 12,671 necropsies performed at the Pathologic Institute of Frankfort. There was 126 cases which were recognized grossly and an additional 64 cases in which the diagnosis was made only by microscopic examination. In his book, Eppinger[6] mentioned 372 cases of cirrhosis seen from 1905 to 1925. The cause of death is given for 135 cases; presumably all were studied post mortem.

Evans and Gray[7] reviewed 17,874 necropsies performed at the Los Angeles County Hospital from January, 1918, to May, 1937, and summarized the cause of death in 217 cases of Laennec's cirrhosis. Halstead and Fainer[10] tabulated the cause of death in 44 cases of cirrhosis culled from the records of 625 consecutive necropsies at the V.A. Center in Los Angeles in 1949. The cause of death is also listed in 58 patients who died during 1951 and 1952 but were not examined post mortem. Hall, Olsen, and Davis[9] noted the cause of death of 782 necropsied cases of portal cirrhosis studied at the Los Angeles County Hospital from 1933

to 1946. These occurred in 16,600 necropsies. Some of these cases (1933 to 1937) are included in the report of Evans and Gray[7].

No attempt has been made to include all of the published cases of cirrhosis. Only the larger series of cases or the better known and widely quoted reports are tabulated. The categories listed are those given by the original authors. Where two categories were listed for a patient (for example, coma precipitated by hemorrhage or infection), the case was listed under the heading of the precipitating factor. These data are summarized and compared with the findings in the present series in Table 1.

**Material and Methods.** A series of 8,676 consecutive necropsies performed at the Queens General Hospital from 1936 to 1950, inclusive, was reviewed. There were 300 cases (3.5%) of portal cirrhosis which form the basis of the present study. Those patients with cardiac (36), obstructive biliary (34), or luetic (3) cirrhosis were excluded from the above group; also excluded was one case of Wilson's disease and 3 cases of hemochromatosis. Thirty-eight patients with limited "cirrhosis" showing no regeneration, little or no fibrosis or distortion of lobular architecture, and varying degrees of fatty infiltration were not included in this study. Patients with hepatitis, due to any agent, were not included, unless there was an underlying cirrhosis of the liver. The uniformity in the evaluation and categorization of this series is emphasized by the review of the historical data, gross organs, histologic sections, and classification of each case by one of the authors (A.A.A.) within one or two weeks of the time of necropsy examination. No attempt was made to differentiate varieties of cirrhosis (for example, postnecrotic, nutritional, and others) for the purpose of this study, since such segregation was not found in the previous reports which were tabulated. In the present paper no discussion of the biochemical, endocrine or other mechanisms involved in causing death is included.

**Results and Comment.** The present series of cases is summarized in Tables 1 and 2. The age and sex distribution in this series closely parallels the totals for the cause of death categories given in the tables. The age distribution is representative of other reported series and also emphasizes the frequency of this disease in older patients whose care is a subject of increasing current concern.

Table 1 emphasizes the considerable variation in the figures reported from different series of cases. This variation appears to be more marked in cases based on clinical diagnoses, with postmortem confirmation of few or no cases. Conversely, there is greater uniformity of results in necropsied series of patients.

In the clinical series a much higher proportion of deaths are categorized as liver failure than in studies based on postmortem examination. This is also true of bleeding esophageal varices since without necropsy confirmation this category includes cases of gastrointestinal hemorrhage due to other lesions such as bleeding peptic ulcer which are not uncommon in cirrhotic patients. Studies based only on clinical examination often overlook significant infection and such cases may then be characterized as due to liver failure rather than infection. Thus in the clinical groups death due to infection is only one-half as frequent as in the necropsy groups, but death due to hepatic coma and bleeding esophageal varices is approximately twice as frequent. Similarly, fatal tuberculosis may not be recognized clinically. Clinical reports rarely include examples of primary carcinoma of the liver or portal vein thrombosis and these cases fail to receive due attention in many reviews. The smaller number of necropsied cases in the miscellaneous category is due to clinical inadequacies as well as the usual selection for clinical studies of symptomatic

cirrhotic patients, whereas the series based on postmortem studies includes all, unselected, cases of portal cirrhosis. This factor of case selection also helps to account for the different frequencies of death due to liver failure, bleeding esophageal varices and infection.

Bockus[3] assigns one-third of the deaths to hemorrhage and two-thirds to progressive failure of the liver where cirrhosis was the direct cause. The tabulated series of cirrhotic patients shows that liver failure and bleeding esophageal varices are responsible for death in approximately equal numbers of patients. Thus of all patients with portal cirrhosis, liver failure and bleeding esophageal varices each accounted for 15 to 20% of all deaths; infection and miscellaneous diseases (particularly cardiovascular and cerebral) were each responsible for 25 to 30% of the fatalities. Since most of the included cases died before the antibiotic era, a considerable diminution of deaths due to pyogenic and tuberculous infections may be expected. It remains to be seen what effect recent therapeutic measures have on the incidence of, and mortality from, bleeding and hepatic coma; future comparison with the present data will aid such evaluation. No notable change in the final total death toll may be apparent because of the large number of patients falling into these categories who formerly died of infection. An increase in postoperative deaths may be anticipated with more frequent surgical procedures for cirrhosis as well as the more common application of surgery generally. Previous reports usually fail to mention death due to trauma as a separate category. In the present series this was responsible for 16 deaths (5%) and was usually attributable to concomitant alcoholism. With increasing longevity many of the incidental degenerative diseases may assume a greater role in the future. If cirrhosis becomes less significant as a direct obvious cause of death it may well become more important as a contributory factor in death due to other diseases; in such cases its role will be more subtle and

TABLE 2.—CAUSE OF DEATH IN 300 PATIENTS WITH PORTAL CIRRHOSIS

| | *Deaths Directly Due to Cirrhosis* | | *% of All Deaths* |
|---|---|---|---|
| | *Number* | *%* | |
| Liver Failure | 50 | 38 | 17. |
| Bleeding Esophageal Varices | 63 | 48 | 21. |
| Primary Carcinoma of the Liver | 13 | 10 | 4. |
| Thrombosis of the Portal Vein or Branches | 5 | 4 | 3. |
| Total | 131 | 100 | |
| | *Death Not Directly Attributable to Cirrhosis* | | |
| | *Number* | *%* | |
| Infection | 60 | 35 | 20. |
| Tuberculosis | 10 | 6 | 3. |
| Cardiovascular, Renal, Cerebral | 42 | 25 | 14. |
| Carcinoma | 15 | 9 | 5. |
| Trauma | 16 | 9 | 5. |
| Postoperative | 13 | 8 | 4. |
| Miscellaneous | 13 | 8 | 4. |
| Total | 169 | 100 | 100. |

difficult to evaluate. A more fundamental answer to these questions will be found only when there is more basic understanding of the mechanisms of hepatic coma and hemorrhage from esophageal varices.

**Summary and Conclusions.** Of 8,676 consecutive necropsies performed at the Queens General Hospital from 1936 to 1950, inclusive, there were 300 cases of portal cirrhosis (3.5%).

One hundred and thirty-one (43%) were directly attributable to the liver disease. These included 63 patients who died from bleeding esophageal varices, 13 from primary carcinoma of the liver, 5 from thrombosis of the portal vein or its branches; in 50 cases death was due to liver failure. Cirrhosis was a significant contributory disease in many additional cases.

These cases were tabulated and compared with more than 2,300 previously reported cases of cirrhosis. Considerable variation in the clinical series and greater uniformity in the series based on necropsy examination were noted. By comparison with patients studied at necropsy the clinical series stressed the frequency of deaths due to liver failure and bleeding esophageal varices; the significance of infection as a cause of death was under-emphasized. This was due to clinical inadequacies as well as the different criteria used for the selection of cases.

A summary of these cases indicates that liver failure and bleeding esophageal varices each accounted for 15 to 20% of all deaths in patients with portal cirrhosis; infection, and miscellaneous causes (particularly cardiovascular and cerebral) were each responsible for 25 to 30% of the fatalities.

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*(Interlingua on page 70)*

# CARDIAC COMPLICATIONS OF INFECTIOUS MONONUCLEOSIS. A REVIEW OF THE LITERATURE AND REPORT OF FIVE CASES

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Infectious mononucleosis, a systemic disease of unestablished etiology, often presents a diversified clinical picture. The pathologic changes are widespread, therefore many diseases may be simulated. The course is frequently mild, even asymptomatic, but prolonged morbidity or death may ensue. The age group 15 to 30 years is usually affected, but reports of cases in the late fifth decade are on record.

Cardiac complications are considered rare. However, there are a number of reports in the literature (Table 1), showing various clinical, electrocardiographic, or postmortem findings accompanying or following infectious mononucleosis. Abnormal electrocardiograms have revealed inverted and flattened T-waves, occasional auriculoventricular conduction blocks, S–T segment depressions, and nonspecific alterations. Clinically, apical systolic murmurs, pericardial friction rubs, and cardiac failure have been infrequently noted.

The incidence of cardiac complications is debatable. Thomsen[28] in 1942 reported that only 8 (1.5%) of 549 cases of infectious mononucleosis showed heart symptoms. Candel and Wheelock[7] in 1945 noted 11 cases with electrocardiographic lowering of the precordial T-waves. In 1946, Wechsler, Rosenblum, and Sills[29] found 53 cases (23%) of 223 patients with the disease having abnormal electrocardiograms. In 1948, Jaffe, Field, and Master[15] reported 9 patients (41%) of 22 cases with abnormal tracings.

Rapaport[25] in 1948 ran electrocardiograms on 8 cases of a series of 43, finding 6 normal, one with pre-existing rheumatic heart disease with atrial fibrillation, and a 23-year-old man with elevated S–$T_{2\text{-}3}$. In a review of 166 cases of infectious mononucleosis, Bennike[3] in 1951 concluded that the tracings were no different from those expected in other acute respiratory diseases. Fifteen patients in a group of 56 were found to have abnormal electrocardiograms by Kalk and Ulbricht[17] in 1951. Shecket[26] in 1955 reported 11 cardiac complications (8%) in 131 cases. In a recent paper, by Hoagland (1956)[14], 100 consecutive hospitalized cases of infectious mononucleosis with one or more electrocardiograms revealed only 5 abnormal tracings.

Transient apical systolic murmurs are reported by Longcope[22] in 1922, Geraghty[13] in 1946, and Leibowitz[20] in 1953. Rheumatic-like vegetations of the mitral valve have been reported from necropsy studies of infectious mononucleosis patients by DuBois (1930)[11], Bradshaw (1931)[5], and Bernstein (1940)[4]. Incidentally, the differential diagnosis between acute rheumatic fever and infectious mononucleosis may be difficult. An occasional victim may have generalized malaise, fever, and arthralgia which may persist several months.

A case of a 22-year-old female who died in the fourth week of infectious mononucleosis of a ruptured spleen and changes in the cardiac muscles was reported by Ziegler[31] in 1944.

Focal necrosis and myocardial infiltrates are reported by Allen and Kellner (1947)[1], Brien (1947)[6], Custer and Smith (1948)[8] and Kass and Robbins (1950)[18]. In a necropsy protocol, Dolgopol and Husson (1949)[10] demonstrated moderate edema and loss of cardiac muscle striation.

A case of first degree heart block was treated by Logue and Hanson[21] in 1944. Two patients with infectious mononucleosis were found to have altered P–R intervals and variations in T-wave height by Young[30] in 1946.

There are very few well-documented cases of acute myocarditis, congestive failure, or acute pericarditis complicating infectious mononucleosis. A case with hepatitis, severe toxemia, and heart failure was reported by Davidsohn (1937)[9]. Jersild (1942)[16] noted severe myocarditis with electrocardiographic S–$T_{2-3}$ depression and death in a 25-year-old man. In 1946 Lyon[23] demonstrated 11 cases with lowered T-waves in the precordial leads. In this series, a 47-year-old female had acute myocarditis. A paper by Bender (1956)[2] described flattened or inverted $T_{3-4}$ in 45% of hospitalized patients with partial restitution in one week and return to normal in 2 or 3 weeks.

Four cases of acute pericarditis accompanying infectious mononucleosis published by Evans and Graybiel (1947)[12] revealed lowered or inverted T-waves in all leads of the electrocardiograms. One of their patients had a massive pericardial effusion. Miller, Uricchio and Phillips[24] reported 3 cases of acute pericarditis in 1953. In the same year, Kramer[19] listed a case of acute pericarditis with recovery. Lastly, Soloff and Zatuchni (1953)[27] reported a case of acute pericarditis as a complication.

**Case Reports.** Five cases of infectious mononucleosis with cardiac complications are herein reported. These cases are as follows:

Case 1. Acute pericarditis and myocarditis.
Case 2. Acute pericarditis.
Case 3. Acute pericarditis, myocarditis, and congestive heart failure.
Case 4. Acute myocarditis, acute hepatitis, and pneumonitis.
Case 5. Acute myocarditis.

CASE 1. A.D. Infectious mononucleosis complicated by acute pericarditis and myocarditis.

July 23, 1948. This 17-year-old white male student entered the hospital with a history of sore throat, swollen neck, fever and chills for 3 days. He had experienced photophobia, orbital headache, nausea, sweats, and temperature 104° F. the day of admission.

Physical examination revealed an acutely ill boy with temperature 102.4° F., pulse 110, respirations 26. There was enlargement of the cervical, axillary, and inguinal nodes. A generalized vesicular eruption was present. The lungs were clear to percussion and auscultation. The heart was normal in size, no arrhythmias were present. A harsh pericardial friction rub persisted for 6 days. A mitral systolic murmur was heard.

The admission leukocyte count was 9,000 with 56% lymphocytes many of which were abnormal. During hospitalization for 6 weeks, the white blood count rose to 13,400 with 71% lymphocytes the majority of which showed vacuolated cytoplasm. The titer of the heterophil antibody test ranged from 0 upon admission to 1:896 before discharge.

Three electrocardiograms revealed inverted $T_{1-3}$ and in the chest leads. These changes persisted for 3 months.

Routine agglutinations, blood, stool, urine cultures and Kahn test were normal. Throat cultures were not remarkable. The sedimentation rate varied from 13 to 24 mm. Roentgenogram of the chest was normal.

There was a febrile course with spikes to 103.4° F. for 2 days, then afebrile for 4 days, finally becoming febrile for 2 weeks (Fig. 1).

Cervical lymphadenitis persisted for 6 months with return of normal blood findings thereafter. Serial electrocardiograms have disclosed no further abnormalities.

CASE 2. J.L. Infectious mononucleosis with acute pericarditis.

December 29, 1951. This 57-year-old white night watchman was admitted to the hospital with a history of headache, sore throat, nausea and vomiting for 3 weeks. Three days previously he had

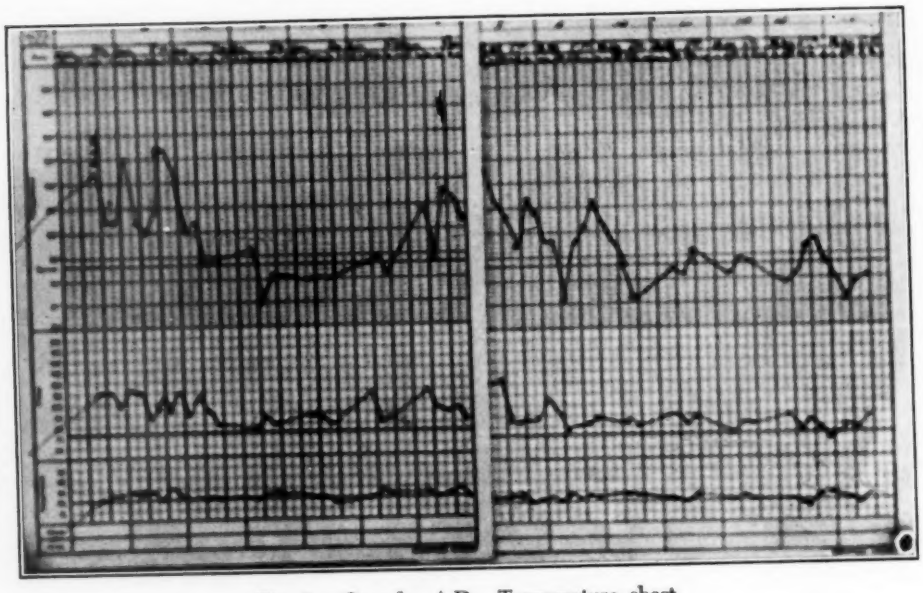

Fig. 1.—Case 1. A.D. Temperature chart.

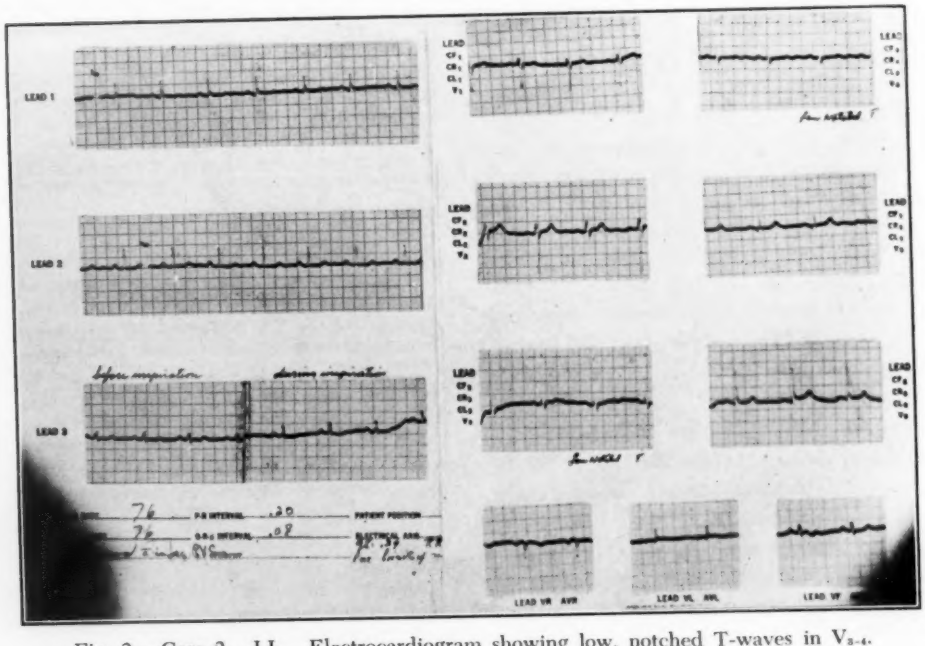


Fig. 2.—Case 2. J.L. Electrocardiogram showing low, notched T-waves in $V_{3-4}$.

experienced substernal pain accompanied by dyspnea. He had fallen from a ladder 10 days earlier.

Physical examination revealed a well-developed and well-nourished man with temperature 100° F., pulse 100, respirations 18, complaining of chest pain. The blood pressure was 135 systolic, 90 diastolic. The pharynx was slightly injected. There were tender palpable cervical lymph nodes bilaterally. The chest was symmetrical and expanded adequately. The lungs were resonant. Vesicular breath sounds and a few subcrepitant rales were audible posteriorly in the region of the angle of the right scapula. The heart was normal in size by percussion. The heart sounds were distant. Rhythm was regular. No murmurs were present. The remainder of the examination was nonrevealing.

Roentgenological films of the skull, cervical spine, and chest were not remarkable.

Admission electrocardiogram was normal. However, serial tracings were indicative of active myocardial or pericardial disease. There was sinus rhythm. P–R interval was 0.19 to 0.20 sec., Q–S interval 0.06 to 0.08 sec. T-waves were low and notched in $V_{3-4}$ (Fig. 2).

The sedimentation rate varied from 25 to 23 mm. The leukocyte count December 31, 1951, was 6,000 with differential count of 59% polymorphonuclears, 38% lymphocytes. Hemoglobin was 14 gm., erythrocyte count 4,580,000. The heterophil antibody test was 1:112. Routine agglutinations, blood culture, fasting blood sugar, urine culture, Kahn test were normal. The throat smear was not remarkable. The serum chloride was 110 mEq./ml. Spinal fluid examination was normal.

On January 5, 1952, the leukocyte count was 4,500 with differential count of 58% segmented cells, 2% eosinophils, 40% lymphocytes (many abnormal). The heterophil antibody test was 1:640.

January 7, 1952, the leukocyte count was 4,350 with differential counts as follows: 2% eosinophils, 40% polymorphonuclears, and 56% lymphocytes resembling Downey number 2 type. The heterophil antibody titer had risen to 1:960.

CASE 3. W.L. Infectious mononucleosis with simultaneous acute pericarditis, myocarditis and congestive heart failure.

This 30-year-old married, white woman entered the hospital February 15, 1950, complaining of dyspnea of 15 days' duration. She was previously admitted January 30, 1950, for ruptured right tubal pregnancy, resulting in right salpingectomy. She was transfused with 1000 ml. whole blood; otherwise her hospital course was uneventful.

She had noted progressive dyspnea, swelling of the ankles, palpitation, and epigastric soreness. There had been concurrent flatulence, but no nausea and vomiting. Two days before admission, she had bitemporal headaches and fever. She had complained of sore throat for 10 days. Review of systems was otherwise negative.

Physical examination disclosed a well-developed and well-nourished young woman with marked orthopnea. There was no cyanosis, cough, or sputum. There was slight bilateral papilledema. The tonsils were moderately enlarged, boggy, injected. There were several soft, freely movable pea-sized lymph nodes in the neck and axillae bilaterally. Many fine moist rales were heard in both lung bases, and there was free fluid in both pleural cavities. The right upper quadrant was tender, but the liver was not palpable. No ascites was present. There was a two plus pre-sacral and pedal edema. The heart was normal in size. A gallop rhythm was present. A blowing systolic mitral murmur was heard. Blood pressure was 180 systolic, 100 diastolic.

A roentgenogram of the chest revealed the heart to be at the upper limits of normal, a small amount of free fluid in both pleural cavities, and signs of passive congestion.

Electrocardiograms were abnormal, and indicative of myocardial disease. P–R interval was 0.14 to 0.15 sec., Q–S interval 0.05 sec., and Q–T interval 0.40 sec. The positive findings were inverted $T_1$, flat or depressed $T_2$, slightly depressed S–$T_2$, diphasic or low $T_3$, diphasic $TV_2$, diphasic $TV_4$, and low notched $TV_5$.

The erythrocyte count was 3,910 000, hemoglobin 12.3 gm., leukocyte count 6,650 with differential count as follows: eosinophils 2%, segmented cells 53%, lymphocytes 43% (most abnormal), and monocytes 2%. The highest leukocyte count was 10,700. The nonprotein nitrogen was 33 mg. per 100 ml., fasting blood sugar 112, cholesterol 146, carbon dioxide combining-power 58 volume %, total serum protein 8.1 gm. serum albumin 3.8, globulin 3.8 A/G ratio 1.1/1. The serum calcium was 11.3 mg. per 100 ml., serum phosphorus 4.3, serum chloride 440 mg. per 100 ml. Blood and urine cultures, routine agglutinations were negative. Icteric index was 2.6 units.

The titer of heterophil antibody test rose from 1:112 to 1:640 with complete absorption by beef cells.

She was placed on a sodium-free diet,

bed rest, digitalized, and given diuretics with progressive improvement. She was discharged on the tenth hospital day.

May 12, 1950, the electrocardiogram showed the same changes (Fig. 3). She was continued on digitoxin, mg. 0.1 daily. The mitral murmur was less marked.

June 11, 1953, electrocardiogram, chest film, heterophil test, complete blood counts, liver function series were normal. The heart sounds were normal, rhythm was regular, and no murmur was present.

lymph nodes were enlarged, discrete, and tender. Examination of the chest showed a few fine moist rales in the left lung base anteriorly, but no alteration in breath sounds or resonance. The heart was normal in size, and rhythm. No murmurs were audible. Blood pressure was 134/82. There was tenderness in the right upper quadrant. The liver and spleen were not felt.

At this time, the red blood count was 5,050,000; hemoglobin 16.6 gm., leukocytes 4,350; differential count: polymorphonuclears

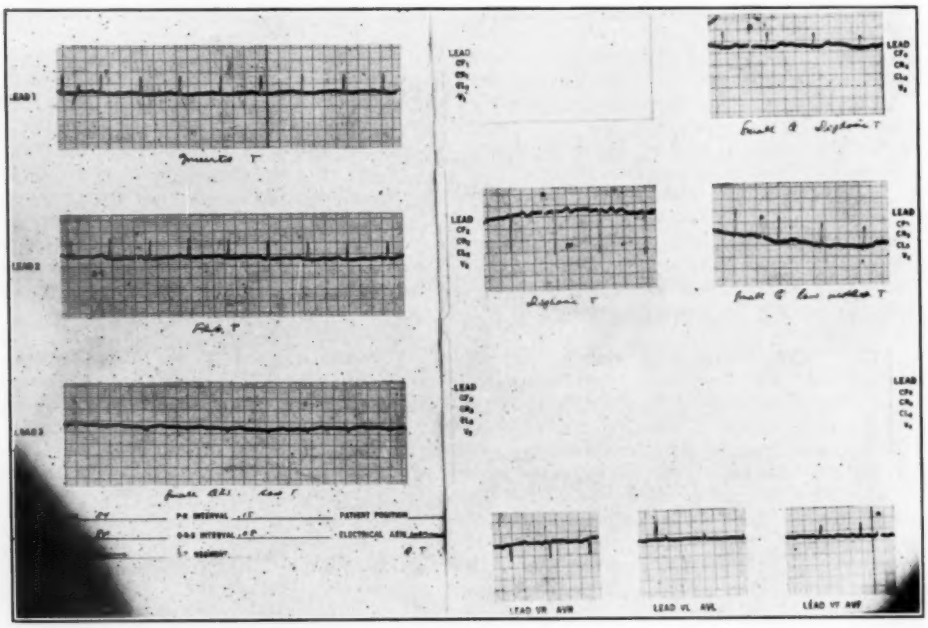

Fig. 3.—Case 3. W.L. Electrocardiogram denoting inverted $T_1$, slight depression of $S–T_2$, low $T_3$, diphasic $TV_2$ and $TV_4$, and low, notched $TV_5$.

CASE 4. R.W. Infectious mononucleosis with acute myocarditis, acute hepatitis, and pneumonia of left lower lobe. This 16-year-old white male student was seen July 6, 1954, with a history of generalized malaise, anorexia, nausea, sore throat, and fever of 101° F. for 4 days. For 12 hours, he had a red rash over the body.

Physical examination revealed a well-developed, robust, acutely ill boy with temperature 103.4° F., pulse 104, respirations 24. The skin was hot, dry, and was covered with a generalized maculopapular rash. There was moderate pharyngeal injection without exudate. The cervical, axillary, and inguinal

56%, eosinophils 1%, and lymphocytes 43% (normal appearing). A heterophil antibody test, blood culture, routine agglutinations, liver function tests, VDRL test, and urinalysis were negative. A throat culture was not remarkable. An electrocardiogram was normal. A roentgenogram of the chest revealed a patchy infiltration in the left lower lobe suggestive of atypical pneumonia, normal heart shadow. He was administered tetracycline, mg. 500 every 6 hours.

One week later, July 13, 1954, the patient became jaundiced, much vomiting occurred, generalized lymphadenopathy and a septic fever persisted. The heterophil antibody titer

was now 1:320. The leukocyte count was 6,200, and there was now 68% lymphocytes, most of which were abnormal, conforming to Downey type number 2 cells. The chest film was unchanged. An electrocardiogram had become abnormal, showing low voltage and T-wave flattening in leads 3, $V_2$-$V_4$, and AVL and AVF. A mitral systolic murmur was now heard. The liver had become palpable 4 cm. below the right costal margin, and the spleen was enlarged. The cephalin flocculation test was 1 plus in 24 and 48 hours, the serum alkaline phosphatase 10 Bodansky units, total serum bilirubin 2.4 mg. per 100 ml., urine urobilinogen 5.2 mg. per 24 hours. The total serum cholesterol was 194 mg. per 100 ml.

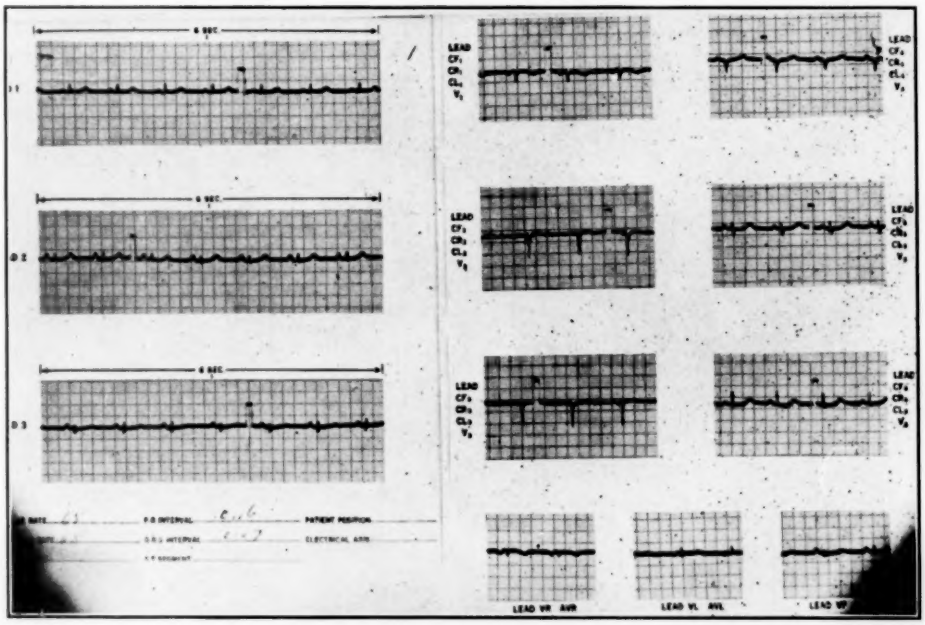

Fig. 4.—Case 4. R.W. Electrocardiogram revealing low voltage, T-lead flattening in leads 3, $V_2$–$V_4$ and AVL and AVF.

The same electrocardiographic changes (Fig. 4) persisted 4 months, then reverted to normal. Serial tracings for 18 months have shown no further changes. Likewise, the liver function tests returned to normal in 3 months. The mitral systolic murmur persisted for 6 weeks. The maculopapular rash disappeared in 6 days. There was a progressive rise of heterophil antibody titer to 1:6,000 with complete absorption by beef erythrocytes, but not by guinea pig kidney suspension.

CASE 5. E.R. Infectious mononucleosis complicated by acute myocarditis. This 17-year-old boy was referred for treatment of a fever of unknown origin of 2 weeks' duration. The temperature had fluctuated from 99.8° to 103.2° F. daily with several chills. There had been a slight sore throat, headache, generalized aching, anorexia, and grabbing pain in the left chest. Past history was not remarkable.

The patient did not appear particularly ill. The skin was warm and dry. The pharynx was mildly injected. The cervical lymph nodes bilaterally were palpable and somewhat tender. The lungs were clear to percussion and auscultation. Heart sounds were regular, and no murmurs were detected. Blood pressure was 130/82. Liver and spleen were not palpable. No other abnormal findings were present.

The heterophil titer was 1:640 with complete absorption by beef cells, slight with guinea pig cells. Routine agglutinations, blood culture, Kline test, fasting blood sugar,

nonprotein nitrogen, urinalysis, and stool culture were normal. The leukocyte count fluctuated from 6,400 to 8,850 with 68 to 84% abnormal lymphocytes.

Serial electrocardiograms revealed prolonged Q–T interval, and lowered flattened, or inverted $T_1$, $T_2$, $T_3$, $TV_{4-6}$, AVL, AVF, suggestive of myocarditis or pericarditis (Fig. 5). These reverted to normal in 6 weeks.

The patient became afebrile after 4 weeks. The heterophil titer was found to be 1:1,280 at the end of 6 weeks. Recheck in 4 months found the heterophil test to be negative.

heart may be affected more often than usually suspected.

The 5 cases described typify the cardiac complications which frequently occur. There were four males and one female white patients. The ages were 16, 17, 17, 30, 57. A harsh pericardial friction rub persisted in Case 1 for 6 days. Mitral systolic murmurs were present in Cases 1, 3, and 4. Congestive heart failure appeared in Case 3.

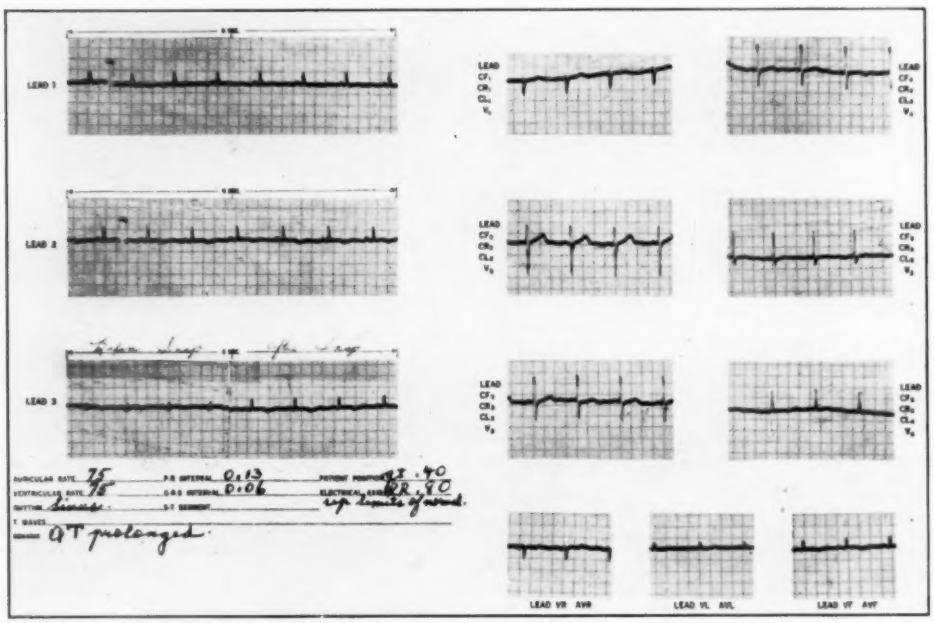


Fig. 5.—Case 5. E.R. Electrocardiogram revealing prolonged Q–T interval, lowered, flattened, or inverted $T_1$, $T_2$, $T_3$, $TV_{4-6}$, AVL, AVF.

**Discussion.** There has been a notable lack of agreement in the literature concerning clinical and electrocardiographic findings in infectious mononucleosis. Proper correlation between the clinical, hematological, and serological essentials of the disease clarifies the diagnosis. The present cases were proven by increasing titers of the heterophil antibody tests and by beef cell absorption. Even though rare, the Severe precordial pain was the chief complaint in Case 5.

Among these 5 cases, electrocardiographic evidence of acute pericarditis was found in Case 2; acute myocarditis and acute pericarditis in Cases 1 and 3; and acute myocarditis in Cases 4 and 5. Case 4 was also complicated by acute hepatitis. The rare complication of acute pneumonitis was present in Case 4. The cardiac involvement

cleared in the cases in 6 weeks to 4 months leaving no apparent residue.

The serious side-effects of infectious mononucleosis makes the proper diagnosis mandatory. Cardiac abnormalities should be treated by bed rest until serial tracings indicate that the process is quiescent. The fact that the etiologic agent has never been isolated precludes any specific therapy.

**Summary and Conclusions.** A review of the literature concerning cardiac complications of infectious mononucleosis is discussed.

Five cases of cardiac involvement in infectious mononucleosis proven by hematological and serological criteria are presented.

The cases include 4 white males and 1 female. These include a 17-year-old boy with acute pericarditis and myocarditis; a 57-year-old man with acute pericarditis; a 30-year-old female with acute myocarditis, hepatitis, and pneumonitis; and finally a 17-year-old boy with acute pericarditis.

All cases were self limited, clearing spontaneously in 6 weeks to 4 months. Treatment was symptomatic, bed rest, and supportive.

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## SUMMARIO IN INTERLINGUA

### Complicationes Cardiac de Mononucleosis Infectiose Revista del Litteratura e Reporto de Cinque Casos

Le litteratura del complicationes cardiac de mononucleosis infectiose es discutite summarimente.

Es presentate cinque casos de mononucleosis infectiose con affectiones cardiac secundo criterios hematologic e serologic.

Le serie include 4 masculos blanc e un feminina blanc. Un del patientes esseva un puero de 17 annos de etate con pericarditis acute e myocarditis; le secunde esseva un homine de 57 annos con pericarditis acute; le tertie un femina de 30 annos con myocarditis acute, hepatitis, e pneumonitis; le quarte un puero de 16 annos con acute myocarditis, acute hepatitis, e pneumonitis; e le ultime un puero de 17 annos con pericarditis acute.

Omne le casos esseva auto-limitante. Omnes se resolveva spontaneemente intra 6 septimanas a 4 menses. Le tractamento esseva symptomatic. Esseva prescribite allectamento e mesuras supportative.

## SUMMARIO IN INTERLINGUA

*(See page 56 for original article)*

### Causa de Morte in Patientes con Morbo de Laennec

Inter le 8.676 necropsias consecutive executate ab 1936 usque al fin de 1950 al Hospital General Queens, 300 casos de cirrhosis portal esseva constatate. Isto amontava a 3,5 pro cento.

Cento trenta-un del mortes post cirrhosis portal esseva directemente attribuibile al disordine hepatic. Iste casos includeva 63 patientes qui moriva ab sanguination de varices esophagee, 13 qui moriva ab carcinoma primari del hepate, 5 qui moriva ab thrombosis del vena portal o su brancas, e 50 in qui le morte esseva causate per disfallimento hepatic. In multe casos additional, cirrhosis esseva un significative factor contributori.

Le casos esseva tabulate e comparate con plus que 2.300 previemente reportate mortes post cirrhosis. Considerabile grados de variation in series reportate super le base de observationes clinic e un plus alte grado de uniformitate in series basate super examines necroptic esseva notate. In comparation con le series studiate per examines necroptic, le series a base clinic superaccentuava le frequentia de mortes causate per disfallimento hepatic e per sanguination de varices esophagee e subaccentuava le signification de infectiones como causas mortal. Isto esseva explicabile per inadequatias clinic e etiam per differentias in le criterios usate in le selection del casos.

Un summario del casos indica que disfallimento hepatic e sanguination de varices esophagee es responsabile, le un e le altere, pro 15 a 20 pro cento de omne mortes in patientes con cirrhosis portal. Infectiones e causas miscellanee (specialmente cardiovascular e cerebral) esseva responsabile, cata un, pro 25 a 30 pro cento del mortes.

# THE EFFECT OF ACETAZOLEAMIDE (DIAMOX) AND AMMONIUM CHLORIDE ON ACID-BASE BALANCE IN PULMONARY EMPHYSEMA: A COMPARATIVE STUDY

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Previous investigators (Bell, Smith Andreae[1], Heiskell, Belsky and Klaumann[3], Lyons, Zuhdi and Kidd[4], Nadell and Kalinsky[5], Schwartz, Relman and Leaf[6], and Taymor, Minor and Friedberg[7]) have shown that when a carbonic anhydrase inhibitor, acetazoleamide (Diamox), is administered to patients with pulmonary emphysema, a lowering in pH and bicarbonate concentration of venous plasma and in pH, $pCO_2$ and bicarbonate concentration of arterial plasma is produced. Since the administration of Diamox to patients with pulmonary emphysema superimposes a metabolic acidosis upon a pre-existing respiratory acidosis, it appeared paradoxical that many of these patients should show symptomatic improvement with this therapy. The improvement has been attributed to increased alveolar ventilation as indicated by the observed decrease in arterial $pCO_2$ (Bell, Smith and Andreae[1], and Lyons, Zuhdi and Kidd[4]).

This report deals with a comparison of the effects of $NH_4Cl$ and Diamox on pH, $pCO_2$, and bicarbonate concentration of venous and arterial plasma in pulmonary emphysema. If changes in these values similar to those produced by Diamox should be observed with $NH_4Cl$, it would follow that these changes cannot be invoked to account for the improvement observed with Diamox since similar improvement is not produced with $NH_4Cl$.

**Methods.** Adult patients who had clinical and radiological evidence of pulmonary emphysema were used in this study. All were on a salt-restricted diet. Blood samples were taken in the morning before breakfast, no food having been allowed the patient after the prior evening meal. Water was permitted *ad libitum*.

Four groups of patients, all at the Douglas County Hospital Annex, were treated as follows:

*Group I*, consisting of 6 male patients, who each received 10 mg. of Diamox per kg. of body weight per day for 7 days. Venous blood was used for analysis.

*Group II*, consisting of 4 male patients, who each received 4 gm. of $NH_4Cl$ per day for 4 days. Venous blood was used for analysis.

*Group III*, consisting of 6 male patients was treated similarly to Group I except that arterial blood obtained by femoral puncture was used for analysis.

*Group IV*, consisting of 4 male patients, was treated similarly to Group II except that arterial blood obtained by femoral puncture was used for analysis.

Samples of blood were taken before and

at the end of each experimental period. Blood plasma was obtained from whole blood anaerobically by the method of Davenport[2]. Total $CO_2$ content was determined by the method of Van Slyke and Stadie[8]. Blood pH determinations were made at 37° C. by means of the Beckman Blood Electrode Assembly (290–31). Values for bicarbonate concentration and $pCO_2$ were calculated by means of the Henderson-Hasselbalch equation from pH and $CO_2$ content, employing a pK of 6.1.

and IV, respectively. It is apparent that $NH_4Cl$ and Diamox produced similar effects on arterial plasma in the two patient groups. Bicarbonate concentration invariably decreased, while pH failed to show a decrease in only one patient who received $NH_4Cl$. The arterial $pCO_2$ either remained unchanged or decreased in the two groups.

TABLE 1.—EFFECT OF DIAMOX ON pH, $pCO_2$ AND $HCO_3^-$ OF VENOUS PLASMA

*Patient Group I*

| | *pH* | | *$pCO_2$ (mm. Hg)* | | *$HCO_3^-$ Conc. (vol.%)* | |
|---|---|---|---|---|---|---|
| *Patient* | *Initial* | *Final* | *Initial* | *Final* | *Initial* | *Final* |
| 1a | 7.45 | 7.25 | 39 | 43 | 59.2 | 40.2 |
| 2a | 7.42 | 7.34 | 44 | 40 | 61.2 | 46.4 |
| 3a | 7.50 | 7.35 | 37 | 36 | 62.7 | 43.0 |
| 4a | 7.40 | 7.32 | 44 | 49 | 58.0 | 54.4 |
| 5a | 7.28 | 7.22 | 66 | 65 | 67.0 | 57.1 |
| 6a | 7.31 | 7.22 | 66 | 62 | 71.5 | 55.0 |

TABLE 2.—EFFECT OF AMMONIUM CHLORIDE ON pH, $pCO_2$ AND $HCO_3$ OF VENOUS PLASMA

*Patient Group II*

| | *pH* | | *$pCO_2$ (mm. Hg)* | | *$HCO_3^-$ Conc. (vol.%)* | |
|---|---|---|---|---|---|---|
| *Patient* | *Initial* | *Final* | *Initial* | *Final* | *Initial* | *Final* |
| 1b | 7.38 | 7.30 | 55 | 62 | 70.0 | 66.2 |
| 2b | 7.44 | 7.22 | 48 | 63 | 70.5 | 55.8 |
| 3b | 7.35 | 7.25 | 57 | 50 | 68.1 | 47.9 |
| 4b | 7.40 | 7.27 | 48 | 58 | 64.9 | 57.9 |

**Results and Discussion.** Tables 1 and 2 show the results of the study carried out in Groups I and II, respectively. With Diamox therapy the bicarbonate and pH values were lowered in all 6 patients. The $pCO_2$ does not show any apparent trend. Ammonium chloride produced about the same lowering in pH and bicarbonate as Diamox. Again, no consistent trend in $pCO_2$ was observed.

Tables 3 and 4 show the results of the study carried out in Groups III

These data suggest that Diamox and ammonium chloride, presumably through the production of a metabolic acidosis, have the same end result on $pCO_2$ in arterial blood of patients with pulmonary emphysema. We can, therefore, assume that the alveolar $pCO_2$ may be lowered in the emphysematous patient with either treatment. In view of these findings the symptomatic relief found with Diamox and not with ammonium chloride in pulmonary emphysema cannot be attributed to lowering

of alveolar $pCO_2$. The improvement found with Diamox must be due to some other effect not yet identified.

**Summary.** Administration of Diamox and ammonium chloride to patients with pulmonary emphysema tended to produce the same lowering of arterial $pCO_2$. The beneficial effect found with Diamox and not with ammonium chloride in these patients must then be attributed to some other unknown effect of Diamox.

TABLE 3.—EFFECT OF DIAMOX ON pH, $pCO_2$ AND $HCO_3^-$ OF ARTERIAL PLASMA

*Patient Group III*

| | *pH* | | *$pCO_2$ (mm. Hg)* | | *$HCO_3^-$ Conc. (vol.%)* | |
|---|---|---|---|---|---|---|
| *Patient* | *Initial* | *Final* | *Initial* | *Final* | *Initial* | *Final* |
| 1c | 7.40 | 7.36 | 50 | 50 | 67.2 | 60.6 |
| 2c | 7.38 | 7.31 | 48 | 43 | 61.4 | 46.9 |
| 3c | 7.41 | 7.35 | 43 | 35 | 58.8 | 41.7 |
| 4c | 7.43 | 7.34 | 42 | 37 | 59.7 | 43.4 |
| 5c | 7.44 | 7.40 | 34 | 31 | 50.3 | 41.5 |
| 6c | 7.45 | 7.32 | 40 | 37 | 59.3 | 41.5 |

TABLE 4.—EFFECT OF AMMONIUM CHLORIDE ON pH, $pCO_2$ AND $HCO_3^-$ OF ARTERIAL PLASMA

*Patient Group IV*

| | *pH* | | *$pCO_2$ (mm. Hg)* | | *$HCO_3^-$ Conc. (vol.%)* | |
|---|---|---|---|---|---|---|
| *Patient* | *Initial* | *Final* | *Initial* | *Final* | *Initial* | *Final* |
| 1d | 7.47 | 7.43 | 39 | 34 | 60.9 | 48.7 |
| 2d | 7.38 | 7.33 | 54 | 45 | 69.2 | 52.1 |
| 3d | 7.44 | 7.44 | 37 | 36 | 55.1 | 52.2 |
| 4d | 7.38 | 7.32 | 46 | 38 | 59.0 | 42.7 |

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## SUMMARIO IN INTERLINGUA

### Le Effecto de Acetazoleamido (Diamox) e Chloruro de Ammonium Super le Balancia Acido-Basic in Emphysema Pulmonar: Un Studio Comparative

In patientes con emphysema pulmonar, le administration de Diamox e le administration de chloruro de ammonium tendeva a effectuar le mesme reduction del $pCO_2$ arterial. Le effecto benefic que es constatate in iste patientes post Diamox sed non post chloruro de ammonium debe per consequente esser attribuite a un altere e non ancora cognoscite effecto de Diamox.

# CLINICAL EVALUATION OF PEGANONE, A NEW ANTICONVULSANT*

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AND

M. C. Maley, M.D.

The search for more effective, less toxic antiepileptic medications is constantly bringing to light new compounds. Additions to the present range of drugs may be of great value to the clinician, since no medication is universally effective in the treatment of the epilepsies, and none is entirely free from the dangers of side effects.

About two years ago a new, synthetic compound, 3-ethyl-5-phenylhydantoin, became available for clinical trial. This compound, known first as AC-695 and later as Peganone, had shown considerable promise in laboratory studies. In mice, doses of 300 to 400 mg./kg. protected against supramaximal electric shock and also against metrazol induced seizures. Double this dose (80 mg./kg.) produced sleep but no other adverse effects. Studies on mice and dogs in which the drug was given continuously for up to 36 weeks showed no toxic effects, and in particular no evidence of damage to the liver, kidneys or blood-forming organs.

Earlier reports (Livingstone and Sweet[2] and Peterman[3]) indicated that a related compound, 3-methyl-5-phenylhydantoin, possessed desirable anticonvulsant properties, but these were associated with toxic effects in some patients. Peganone is derived by substitution of an ethyl group for the methyl in this earlier compound. There is evidence that this substitution very materially reduces the toxicity. A clinical report by Schwade, Richards and Everett[4] supports this evidence, since they state that Peganone is an effective drug which has less side effects than any anticonvulsant in their experience.

**Material and Method:** This investigation was commenced in April, 1955, and is still continuing. Since detailed records are kept of all seizures which occur in the institution in which this study was carried out, it is possible to make very precise comparisons between the degrees of control obtained with and without Peganone.

The patients selected for this study were those suffering from mixed grand mal and petit mal epilepsy. Cases with psychomotor and other variants were excluded. All patients had every seizure recorded for a control period of one year before treatment with Peganone was commenced.

In evaluating the results it was decided to eliminate seizures which occurred during *status epilepticus* from both the control and treatment periods. There were two reasons for this decision. First, it is difficult to count precisely the number of separate seizures which occur during an episode of *status*. Often, only an estimate can be made which varies with the interpretation of the observer. Secondly, it has been our experience that any radical change in medication is likely to be followed by an increased incidence of *status*.

It is believed that a better impression is obtained of the degrees of control by recording all seizures which occur independently of episodes of *status*. Notwithstanding this reservation, it was our definite impression that once satisfactory control with Peganone was obtained the number of episodes of *status* was materially reduced as compared with the control period on other medications.

*This investigation was carried out at the Florida Farm Colony, Gainesville, Florida. The Peganone used in this study was supplied by Abbott Laboratories, North Chicago, Illinois.

Most of the patients studied were children, ranging in age from one year to 18 years; 15 were adults. Of the total of 38, seven were females and 31 were males. The patients were all classified as severe, refractory epileptics, for which reason they required institutional care. Evaluation of a new medication in these patients represented a stringent test. Treatment had already been carried out to the point of maximum benefit with established remedies, alone or in combination.

In 9 cases, Peganone was used alone, but in 29, it was combined with the previous medication. No incompatibilities were found with other antiepileptic drugs. Dosage was commenced at 0.5 gm. daily, and in most cases was gradually increased to a total of 3 to 4 gm. daily, divided into three doses. In a few adults, dosage was carried to a maximum of 5 or 6 gm. daily.

We encountered no toxic effects during this investigation. Complete blood studies,

TABLE 1.—COMPARISON OF SEIZURES DURING CONTROL AND TREATED PERIODS

| | *Control Period* | | | | *Test Period* | | | |
|---|---|---|---|---|---|---|---|---|
| | | *Number of Seizures* | | | | *Number of Seizures* | | |
| *Name* | *Time in Days* | *Grand Mal* | *Petit Mal* | *Total* | *Time in Days* | *Grand Mal* | *Petit Mal* | *Total* |
| E.A. | 366 | 93 | 25 | 118 | 55 | 1 | 0 | 1 |
| A.L.B. | 365 | 64 | 32 | 96 | 446 | 37 | 14 | 51 |
| M.L.B. | 365 | 50 | 114 | 164 | 223 | 15 | 11 | 26 |
| D.B. | 366 | 112 | 63 | 175 | 98 | 25 | 30 | 55 |
| E.B. | 365 | 104 | 24 | 128 | 448 | 44 | 16 | 60 |
| R.C. | 365 | 76 | 38 | 114 | 153 | 7 | 9 | 16 |
| M.C. | 365 | 105 | 21 | 126 | 464 | 102 | 23 | 125 |
| J.C. | 366 | 16 | 11 | 27 | 55 | 2 | 0 | 2 |
| H.E.C. | 366 | 3 | 6 | 9 | 36 | 1 | 0 | 1 |
| O.C. | 366 | 12 | 3 | 15 | 55 | 1 | 1 | 2 |
| H.O.C. | 366 | 18 | 5 | 23 | 55 | 1 | 0 | 1 |
| W.C. | 366 | 116 | 22 | 138 | 75 | 2 | 5 | 7 |
| E.D. | 366 | 6 | 2 | 8 | 55 | 0 | 0 | 0 |
| B.D. | 365 | 74 | 27 | 101 | 448 | 16 | 9 | 25 |
| T.F. | 365 | 85 | 80 | 165 | 448 | 23 | 8 | 31 |
| E.L.G. | 365 | 3 | 1 | 4 | 467 | 38 | 28 | 66 |
| E.D.G. | 365 | 136 | 50 | 186 | 448 | 71 | 36 | 107 |
| M.H. | 365 | 86 | 60 | 146 | 190 | 14 | 9 | 23 |
| J.H. | 366 | 17 | 0 | 17 | 60 | 2 | 1 | 3 |
| P.H. | 365 | 25 | 13 | 38 | 434 | 15 | 2 | 17 |
| E.K. | 365 | 71 | 8 | 79 | 274 | 30 | 0 | 30 |
| N.L. | 365 | 31 | 8 | 39 | 219 | 18 | 8 | 26 |
| J.E.L. | 365 | 10 | 25 | 35 | 190 | 1 | 2 | 3 |
| C.L. | 365 | 220 | 1 | 221 | 160 | 3 | 3 | 6 |
| J.O.M. | 366 | 23 | 4 | 27 | 121 | 3 | 0 | 3 |
| J.A.M. | 366 | 45 | 28 | 73 | 63 | 1 | 0 | 1 |
| G.N. | 365 | 57 | 32 | 89 | 434 | 4 | 7 | 11 |
| H.O. | 365 | 130 | 3 | 133 | 251 | 9 | 6 | 15 |
| R.P. | 365 | 118 | 102 | 220 | 462 | 6 | 0 | 6 |
| C.P. | 365 | 16 | 7 | 23 | 441 | 15 | 9 | 24 |
| H.S. | 365 | 28 | 14 | 42 | 267 | 32 | 23 | 55 |
| L.S. | 365 | 24 | 15 | 39 | 457 | 2 | 2 | 4 |
| R.T. | 366 | 96 | 13 | 109 | 110 | 21 | 3 | 24 |
| B.A.W. | 365 | 125 | 62 | 187 | 245 | 6 | 4 | 10 |
| J.W. | 365 | 45 | 19 | 64 | 232 | 6 | 6 | 12 |
| B.W. | 365 | 92 | 48 | 140 | 462 | 13 | 3 | 16 |
| W.D. | 365 | 10 | 15 | 25 | 219 | 0 | 0 | 0 |
| T.Y. | 366 | 23 | 9 | 32 | 110 | 1 | 0 | 1 |

liver function tests and urinalyses were carried out at the start of the test period, and monthly thereafter. There were no deviations from normal. No case of skin rash was seen, and no patient showed evidence of gum hyperplasia. The only side effect (which was observed in only a few patients) was some drowsiness when dosage was increased above 1.5 gm. t.i.d. Good control was obtained in the majority of cases by a dosage of 3 to 4 gm. per day.

**Results.** The results of this study are set forth in Table 1. It will be seen that 13 patients were studied for a period of well over one year, a further 10 for 6 to 9 months, the remainder (15) for a lesser time. Since there was slight variation in the control period, and wide variations in the test periods, it was necessary to arrive at some common denominator. This was obtained by reducing the seizures to a daily average for both the control and test periods. These figures are shown in Table 2. The final results are given as an over-all average for the entire group in Table 3.

TABLE 2.—AVERAGE DAILY INCIDENCE OF SEIZURES

| *Patient* | *Control Period* | *Test Period* | *Percentage Improvement* |
|---|---|---|---|
| E.A. | 0.32239 | 0.01818 | 94.4 |
| A.L.B. | 0.26301 | 0.11434 | 56.5 |
| M.L.B. | 0.44910 | 0.11658 | 74.0 |
| D.B. | 0.47814 | 0.56122 | −17.4 |
| E.B. | 0.35068 | 0.13392 | 61.8 |
| R.C. | 0.31231 | 0.10457 | 66.5 |
| M.C. | 0.34520 | 0.26938 | 22.0 |
| J.C. | 0.07376 | 0.03636 | 50.7 |
| H.E.C. | 0.02458 | 0.02777 | −13.0 |
| D.C. | 0.04097 | 0.03636 | 11.3 |
| H.O.C. | 0.06284 | 0.01818 | 71.1 |
| W.C. | 0.37703 | 0.09332 | 75.2 |
| E.D. | 0.02185 | 0.00000 | 100.0 |
| B.D. | 0.27670 | 0.05579 | 79.8 |
| T.F. | 0.45204 | 0.13838 | 69.4 |
| E.L.G. | 0.01094 | 0.14132 | −1191.8 |
| E.D.G. | 0.50958 | 0.23883 | 53.1 |
| M.H. | 0.39999 | 0.12104 | 69.7 |
| J.H. | 0.04644 | 0.04999 | −7.6 |
| P.H. | 0.10410 | 0.03916 | 62.4 |
| E.K. | 0.21643 | 0.10948 | 49.4 |
| N.L. | 0.10684 | 0.11871 | −11.1 |
| J.E.L. | 0.09588 | 0.01578 | 83.5 |
| C.L. | 0.60546 | 0.03750 | 93.8 |
| J.O.M. | 0.07376 | 0.02479 | 66.4 |
| J.A.M. | 0.19945 | 0.01587 | 92.0 |
| G.N. | 0.24383 | 0.02533 | 89.6 |
| H.O. | 0.36437 | 0.05975 | 83.6 |
| R.P. | 0.60273 | 0.01298 | 97.8 |
| C.P. | 0.06300 | 0.05441 | 13.6 |
| H.S. | 0.11506 | 0.20599 | −79.0 |
| L.S. | 0.10684 | 0.00874 | 91.8 |
| R.T. | 0.29780 | 0.21817 | 26.7 |
| B.A.W. | 0.51232 | 0.04080 | 92.0 |
| J.W. | 0.17535 | 0.05172 | 70.5 |
| B.W. | 0.38355 | 0.03462 | 91.0 |
| W.D. | 0.06848 | 0.00000 | 100.0 |
| T.Y. | 0.08743 | 0.00909 | 89.6 |

TABLE 3.—OVER-ALL IMPROVEMENT

1. *Total Seizures of 38 Patients*

| *Control Period* | | | *Test Period* | | |
|---|---|---|---|---|---|
| *Grand Mal* | *Petit Mal* | *Total* | *Grand Mal* | *Petit Mal* | *Total* |
| 2365 | 1010 | 3375 | 588 | 278 | 866 |

2. *Total Treatment Days*

| *Control Period* | *Test Period* |
|---|---|
| 13883 | 9430 |

3. *Average Number of Seizures Per Patient Per Day*

| *Control Period* | | | *Test Period* | | |
|---|---|---|---|---|---|
| *Grand Mal* | *Petit Mal* | *Total* | *Grand Mal* | *Petit Mal* | *Total* |
| 0.171 | 0.073 | 0.243 | 0.062 | 0.029 | 0.092 |
| *Percentage Improvement* | | | 63.7 | 60.3 | 62.1 |

**Discussion.** From these figures it will be seen that as a group these patients experienced a 62% reduction in the number of seizures (computed on a daily basis) when on Peganone therapy. The results in grand mal were slightly better (63.7% improvement), and in petit mal a little less (60.3% improvement).

From Table 2 the response of the individual patients can be evaluated. Only one patient of the 38 (E.L.G.) showed marked increase in the number of seizures while on test. One

patient (H.S.) showed a significant increase, 3 others showed a mild increase of less than 20%. In the remaining 33 patients (86.8% of the total) there was improvement.

In 15 patients (35%) there was more than 75% reduction in the number of seizures per day, in the test as compared with the control period. In 12 patients there was a similar reduction of between 50 and 75%. Thus, a total of 27 patients (71% of the group) showed an improvement of over 50%.

Probably, these figures do not completely reflect our great enthusiasm for Peganone. It is perhaps worth re-emphasizing that these patients were chronic and refractory cases. Any additional improvement that can be obtained in this type of case is worth while. When the agent which will bring about such improvement also shows a complete freedom from toxic effects, it should be assured of a place in the routine treatment of the epilepsies. In our experience the control obtained with Peganone has been at least as good as that with diphenylhydantoin.

**Summary and Conclusions.** 1. After a control period of one year on established therapy, 38 chronic, refractory, institutionalized epileptics were treated with 3-ethyl-5-phenylhydantoin (Peganone).

2. Cases were studied suffering from mixed grand and petit mal epilepsy.

3. In the group as a whole there was an over-all improvement of 62% in the number of seizures. Seventy-one per cent of the cases showed a reduction of more than 50% in the number of seizures.

4. Routine blood studies, liver function tests and urinalyses were carried out on all patients. There were no deviations from normal, and no evidence of other toxic effects such as gum hyperplasia or skin rash. The only side effect noted was some drowsiness on very high dosage (in excess of 4.5 gm. daily).

5. A significant improvement in control was achieved in this group by either adding Peganone to the existing regimen, or (in many cases) by its use alone. It is considered that Peganone is a most valuable addition to those drugs currently available because of its effectiveness and lack of toxicity.

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*(Interlingua on page 116)*

# OBSERVATIONS ON SERUM LIPID LEVELS IN RHEUMATIC SUBJECTS AND THEIR SIBLINGS*

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and

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A disturbed lipid metabolism may be a factor in the genesis of rheumatic fever. In 1950, Coburn[3] reported that the human host having a high blood lipid level associated with nephrosis, diabetes mellitus, or following total thyroidectomy seemed to be refractory to rheumatic fever. In contrast, patients with hyperthyroidism and persons receiving therapeutic doses of thyroid extract showed low blood lipid levels and increased susceptibility to rheumatic fever. Scalabrino and Bartsaghi[9] observed that serum cholesterol, and Wallis and Viergiver[15] showed that the serum phospholipid level was low in rheumatic fever subjects. Stollerman *et al.*[12,13] demonstrated that streptolysin inhibitor, which appears to be a phospholipoprotein complex, was low in rheumatic fever subjects.

Nutritional studies of Coburn[2,5] indicated that there appears to be an association between rheumatic susceptibility and a deficiency in the consumption of eggs throughout childhood. It was shown that the feeding of large amounts of whole egg yolk powder may prevent rheumatic recurrences following group A streptococcal throat infections. The present investigations were undertaken to study blood lipid levels in rheumatic families and the effect of a crude egg yolk fraction (alcohol-soluble materials of egg yolk) on the serum lipid levels of rheumatic fever children whose disease process appeared to be quiescent.

Blood lipid levels (fasting) of the rheumatic subjects were tested during a period of their normal diets and at intervals of 3 months after the diet was supplemented with the alcohol-soluble material (ASM) of egg yolk. Sera (fasting) were also obtained from: a) siblings, having approximately the same age as the rheumatic subjects on the supplemented diet; b) other rheumatic fever subjects on their usual diet and their siblings. Each sibling was selected because the child had reached the age of 10 to 15 without developing any clinical or laboratory evidence of rheumatic disease. In all cases the blood samples were taken in the morning prior to breakfast. Determinations on serum samples from rheumatic subjects and siblings were made in parallel.

This study includes 2 years of investigations by two groups of chemists.

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The patients and siblings were approximately the same group each year. The egg yolk alcohol-soluble material (ASM) although prepared in the same manner had less anti-inflammatory protective activity the second year as determined by animal assays. The main difference in the two investigations was the chemical methods. It was felt after the first year that changes should be made in the methods to give results which would be less time-consuming and more reproducible. Observations on the methods and the findings for each of the 2 years of this study are reported.

**Material and Methods.** A. 1954–1955. The procedure used for preparation of alcohol-soluble materials (ASM) from egg yolk was essentially that described by Coburn, Graham, and Haninger[4]. The ASM Lot number was 92276. The fractionation was done by the Wilson Laboratories. For this study, 160 lbs. of ASM (equivalent to 21,167.5 whole egg yolks) were prepared as an elixir and bottled by the Armour Laboratories. Each tablespoonful of the elixir contained 4.5 gm. of ASM, which was equivalent to 1.5 whole egg yolks. Throughout the study the children were given ASM (a pint bottle of elixir) twice each month and advised to take 2 tablespoonfuls in milk for breakfast and again for supper. The prescribed amount of ASM was equivalent to 6 whole egg yolks per day. Only one child consumed the amount prescribed. The average consumption of ASM of these 35 children was equivalent to 3 egg yolks daily.

B. 1955–1956. Wilson Laboratories made 331 lbs. of alcohol-soluble material (ASM, 45.4% solids). For the clinical work 155 lbs. of ASM (equivalent to 21,141 whole egg yolks) were prepared as an elixir which was palatable in milk. This preparation was bottled by Armour Laboratories. Each tablespoonful of the elixir contained 4.54 gm. of ASM, which was theoretically equivalent to 1.53 whole egg yolks. As in the previous year the children were advised to take 2 tablespoonfuls of ASM for breakfast and again for supper, which would have supplied the equivalent of 6 whole egg yolks. Thirty-one patients receiving this product, consumed theoretically the equivalent of 2.2 egg yolks per day. However, by animal assay it was found that this ASM (Lot #95912) had only about 30% of the activity of the 1954 material (Lot #92276).

SUBJECTS. A. 1954–1955. In order to avoid the lowering effects of fever or inflammation on serum lipids we have tested only rheumatic subjects in whom there was no detectible clinical or laboratory evidence of disease activity. Three children were dropped for lack of co-operation and 34 were maintained in the first year's study group. These children lived at home, led their usual lives, and visited the clinic once each month. All 34 subjects had been hospitalized on one or more occasions with frank, severe rheumatic attacks including carditis. It was the opinion that each child had marked susceptibility to rheumatic fever. Most had not reached puberty. The age varied from 4 to 17 with an average of 11.1 years. They came from low income, underprivileged groups and included 27 Negroes and 8 Caucasians. Most of the children came from families with many mouths to feed and a low food budget with a scarcity of eggs in the home. They had a maximum of 14 and a minimum of 2 siblings with an average of 5.5 brothers and sisters living in overcrowded tenements. Besides having an inadequate diet at home, these children were exposed to the common respiratory tract infections which occur in the public schools of Chicago during the winter and spring months.

B. 1955–1956. The 34 children, who had received ASM in 1954–1955 were again selected for this study. For reasons other than health, 3 patients were dropped, leaving 31 in the study group. Of these, there were 18 boys and 13 girls. As stated above, all had been hospitalized on at least one occasion with frank, severe rheumatic attacks; all came from low income, underprivileged groups. The group included 24 Negro and 7 Caucasian children. The first year there were 1,056 patient-weeks and the second year 994 patient-weeks.

CHEMICAL DETERMINATIONS OF BLOOD CONSTITUENTS. A. 1954–1955. Fasting venous blood samples were obtained from the rheumatic children on their usual diet and periodically from these subjects after they had received the ASM supplement for approximately 18 and 29 weeks. Samples were obtained from 21 normal siblings of the rheumatic subjects receiving the ASM supplement. The blood was drawn in the morning before breakfast or any other food was consumed. For comparison, fasting blood samples were obtained in May, 1955, from 17 additional, quiescent rheumatic subjects on their usual diets. The total lipid, lipid

phosphorus and cholesterol findings (mg./ml.) were: 6.7 ± .27, 2.21 ± .08 and 1.43 ± .11. These values were similar to those shown in Table 2.

Serum total lipid was determined by extracting frozen dried serum with hot chloroform and methanol (2:1) in a Soxhlet extractor for 36 hours. The extraction was taken to dryness in a water bath at 40° C. under a stream of nitrogen. The residue was redissolved in chloroform at room temperature and filtered. The total lipid was calculated from the weight of residue remaining after the filtrate was dried to a constant weight. The lipid phosphorus and the total cholesterol in the lipid extraction were determined by the methods of Youngberg and Youngberg as described by Hawk, Oser and Summerson[6] and Zlatkis, Zak and Boyle[16] respectively. Phospholipid values were calculated by multiplying the lipid phosphorus values by 26. The serum total nitrogen was determined by a micro-kjeldahl procedure (Keys[7] and Ma and Zuazaga[8]).

The method of lipid extraction used at first requires prolonged boiling, which is thought by many to decompose lipid, and it does not include purification. During the second year lipid analyses were made with the method of Sperry and Warren[10]. Serum is extracted by shaking with $CHCl_3$:$CH_3$, 2:1, and heating to the boiling point, after which it is filtered, purified with distilled water and washed with $CaCl_2$ solution. Samples of beef serum extracted by both methods gave comparable serum cholesterol and lipid phosphorus results, indicating that none had been lost in purifying. The total lipid figure obtained by the former method showed an average of 6.5 ± 0.31 mg. lipid/ml. serum; whereas samples extracted by the Sperry and Warren method averaged 4.8 ± 0.19 mg./ml. This difference in total lipids is presumably due to removal of nonlipid material during purification. Tests of the wash solutions showed an insignificant loss of total lipid. Furthermore, when samples extracted by the first method were purified, the average total lipid value equalled 4.9 mg./ml.

Scrutiny of the Zlatkis cholesterol method[16] which was used during the first year gave a different interpretation of the significance of the serum blank. Results obtained by subtracting a serum blank were lower than those obtained by the method of Liebermann-Burchard[1]. It appears that either no blank or a corrected one should be subtracted.

Before these methods were used for the rheumatic subjects they were tested on laboratory workers. Fasting serum was drawn biweekly on each of 2 normal young female adults and was analyzed for total lipids, phospholipid and cholesterol. The data indicates that the lipid values for the individual do not fluctuate appreciably from week to week. The methods used in this 1955–1956 series gave reproducible determinations. Observations are shown in Table 1.

TABLE 1.—BIWEEKLY VARIATIONS IN SERUM LIPIDS OF NORMAL SUBJECTS

| *Miss K.V.* | | | *Mrs. P.P.* | | |
|---|---|---|---|---|---|
| *Total Lipid mg./ml.* | *Phosphorus mg./ml.* | *Cholesterol mg./ml.* | *Total Lipid mg./ml.* | *Phosphorus mg./ml.* | *Cholesterol mg./ml.* |
| 6.0 | 0.0825 | 2.31 | 5.8 | 0.0981 | 2.46 |
| 5.8 | 0.0854 | 2.24 | 6.0 | 0.1031 | 2.31 |
| 5.8 | 0.0854 | 2.19 | 6.1 | 0.1032 | 2.38 |
| 6.0 | 0.0821 | 2.24 | 5.9 | 0.0938 | 2.38 |
| Average: | | | | | |
| 6.0 | 0.0835 | 2.25 | 6.0 | 0.0946 | 2.40 |
| 5.9 ± 0.10 | 0.0838 ± .0013 | 2.25 ± 030. | 6.0 ± 0.08 | 0.0986 ± .0036 | 2.39 ± .03 |

**Results.** The supplement of ASM was added to the diets in November, 1954, and continued into 1955 for a period of approximately 33 weeks. The patients were seen at biweekly home and clinic visits. Most of them gained weight from 1 to 20 lbs. with an average of 6.8 lbs. The effect of administering ASM supplement for about 7 months on the serum lipids of the quiescent rheumatic fever children is presented in Table 2. After 18 weeks

on the ASM supplemented diet the serum total lipids, cholesterol and phospholipids of the quiescent rheumatic fever children were higher than when on their customary diets. In contrast to the siblings, they were significantly lower (total lipids $p = .05$, cholesterol $p = .025$, and phospholipids $p = .05$). At the end of the supplementary period (approximately 29 weeks of the ASM supplement) there was a further rise in the phospholipid levels. In this series of observations, the serum phospholipids, but not total lipids or cholesterol, of the quiescent rheumatic fever children was raised to the same level as that of their siblings. Five months after the ASM supplement was discontinued, the serum total lipids, cholesterol and phospholipid levels of the quiescent rheumatic fever children were again determined. The levels which were obtained at this time on normal diets were significantly lower than those which existed when the subjects received the ASM supplement. The serum total nitrogen level was influenced neither by the rheumatic state nor by the ASM supplement. The findings are shown in Table 3.

TABLE 2.—EFFECT OF EGG YOLK ALCOHOL-SOLUBLE MATERIALS (ASM) ON TOTAL LIPID, PHOSOPHOLIPID AND CHOLESTEROL LEVELS IN SERUM OF QUIESCENT RHEUMATIC FEVER CHILDREN, 1954–1955

| Subjects | No. of Subjects | Age Yrs. | Treatment | Ave. Total Lipid mg./ml. | S.E. | Ave. Cholesterol mg./ml. | S.E. | Ave. Phospholipid mg./ml. | S.E. | Season |
|---|---|---|---|---|---|---|---|---|---|---|
| Rheumatic fever subjects | 30 | 4–15 | Normal diet | 6.2 | ± .24 | 1.27 | ± .05 | 1.98 | ± .05 | Fall |
| | 34 | 4–15 | After 3 mos. ASM | 6.7 | ± .22 | 1.45 | ± .06 | 2.13 | ± .05 | Winter |
| | 33 | 4–15 | After 6 mos. ASM | 6.6 | ± .14 | 1.39 | ± .02 | 2.39 | ± .05 | Spring |
| Siblings of rheumatic fever children | 21 | 7–15 | Normal diet | 8.0 | ± .22 | 1.66 | ± .06 | 2.35 | ± .13 | Spring |

TABLE 3.—THE LEVEL OF SERUM TOTAL NITROGEN IN RHEUMATIC SUBJECTS AND THEIR SIBLINGS

| Subjects | No. Subjects | Treatment | Duration Weeks | Ave. Total Nitrogen mg./ml. | S.E. |
|---|---|---|---|---|---|
| Rheumatic fever subjects | 34* | ASM supplement | 18 (12.5–22.5) | 12.87 | ± .10 |
| Siblings | 21 | —— | —— | 12.91 | ± .13 |

*No blood was drawn from patient V.C., hospitalized for bronchitis.

The 1955–1956 investigation was conducted along similar clinical lines as that of the previous year. The sub-

jects were one year older. There was a weight change from a loss in one child of 2 lbs. to a gain of 42 lbs. with an average increase of 10.6 lbs. The increases in the levels of serum lipids during the 6 months of study are shown in Table 4. Within 3 months on the ASM supplemented diet these rheumatic subjects showed significant rises in their cholesterol and total lipid levels and an increase in the lipid phosphorus. A continuation of the ASM for another period of 3 months failed to cause further rises in serum levels. At this time (May–June) the serum values for total lipids, lipid phosphorus and cholesterol were still slightly lower than the values obtained for their siblings whose serum samples were also obtained in May–June and tested in parallel. Prior to supplementing with ASM, the values obtained for these rheumatic subjects had been considerably lower than those of their siblings. For cholesterol and total lipids these differences were statistically significant. The findings are shown in Table 4.

TABLE 4.—EFFECT OF EGG YOLK ALCOHOL-SOLUBLE MATERIALS (ASM) ON TOTAL LIPID, LIPID PHOSPHORUS AND CHOLESTEROL LEVELS IN SERUM OF QUIESCENT RHEUMATIC FEVER CHILDREN, 1955–1956

| *Subjects* | *No. of Subjects* | *Treatment* | *Ave. Total Lipid* mg./ml. S.E. | *Ave. Cholesterol* mg./ml. S.E. | *Ave. Phospholipid* mg./ml. S.E. | *Season* |
|---|---|---|---|---|---|---|
| Rheumatic fever subjects | 34 | Normal diet | °4.5 ± 0.3 | 0.0750 ± 0.0018 | 1.34 ± 0.05 | Fall |
| | | After 3 mos. ASM | 6.1 ± 0.1 | 0.0790 ± 0.0014 | 1.79 ± 0.05 | Winter |
| | | After 6 mos. ASM | 5.7 ± 0.2 | 0.0759 ± 0.0020 | 1.79 ± 0.06 | Spring |
| Siblings of rheumatic fever children | 28 | Normal diet | 5.9 ± 0.2 | 0.0801 ± 0.0021 | 1.86 ± 0.06 | Spring |

°Corrected for method used in 1956 (Stollerman, Brodie and Steele[13]).

**Discussion.** The primary purpose of this study was to determine whether quiescent rheumatic subjects differ from their siblings in serum lipid values. The patients were selected with the belief that each was highly susceptible to a rheumatic recurrence; all had been hospitalized with at least one typical, severe attack of rheumatic fever characterized by carditis and polyarthritis. Each patient had been under clinical observation and was known to have been in good health for at least 6 months prior to this study. The siblings selected were of approximately the same ages as the patients and were known to have repeated nasopharyngeal infections without developing any detectible rheumatic manifestations. Blood determinations on patients and siblings were made only when there was no clinical or laboratory evidence of disease. Although the differences in serum lipid values between rheumatic child and nonrheumatic sibling were not great, the findings indicate that the values of certain serum lipids are low in the quiescent rheumatic subject. This is in accord with the observations of

Wallis[14]. Wallis not only reported a correlation between the low blood level of phospholipids in the rheumatic fever subject and the consumption of eggs but also suggested that the high content of choline (a part of lecithin) in egg may modify the synthesis of serum phospholipids in man. Steiner and Domanski[11] observed that the feeding of whole egg yolk powder to man and dog produced hypercholesterolemia. They were of the opinion that the lecithin content of their egg yolk powder was an important factor in the elevation of serum cholesterol because comparable effects were not obtained by diets rich in fat and cholesterol.

A second objective of this study was to determine whether serum lipid levels can be increased by the addition of egg yolk alcohol-soluble material (ASM) to the diet of the rheumatic subject. A biweekly check by the nurse in charge of this study afforded accurate information on the actual amount of ASM ingested. Within 3 months after the initiation of the dietary supplement of ASM the serum lipid values rose. However, there was no further rise with continued administration of ASM. In each patient, the ASM supplement was discontinued from June until November; the three serum lipid values fell significantly. It was not practicable to risk rheumatic recurrences by giving a placebo to a "control" group. Ancillary serum determinations were made, however, on comparable rheumatic children receiving penicillin prophylaxis (17 in the first year and 42 in the second year). These did not show rises in the serum lipids. In this study the rises in serum lipid levels observed are believed to be associated with the ingestion of egg yolk ASM. This increase was not large in any instance, and the serum lipids did not exceed normal values even after 6 months of the supplemented diet.

In conclusion, this study was not designed to determine whether an increase in serum lipids is helpful to the rheumatic subject. Furthermore, it is not suggested that the serum level of any particular lipid is of significance to the rheumatic state. It is pointed out that the findings in each of 2 years of this study suggest that in the rheumatic subject there may be a metabolic abnormality, one expression of which is a depression of the serum lipid levels. Whether the observed low level of serum lipids is a precursor or sequela of the rheumatic state remains to be determined.

**Summary.** Two investigations were made, using different chemical methods, to determine whether: a) quiescent rheumatic subjects have different serum lipid levels than their nonrheumatic siblings; b) supplementation of the diet with egg yolk alcohol-soluble material (ASM) modifies the serum lipid levels.

Serum lipid values for quiescent rheumatic subjects were found to be lower than those obtained for nonrheumatic siblings of approximately the same ages. For cholesterol and total lipid the difference was statistically significant.

Supplementation of the normal diets with egg yolk ASM was followed by increases in the levels of serum lipids. These increases appeared to reach a peak within 3 months. However, even after 6 months of supplemented diets, the values for the rheumatic children were not as high as those of their nonrheumatic siblings receiving the family diet.

The possibility that rheumatic susceptibility may be associated with an abnormality in lipid metabolism is discussed.

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## SUMMARIO IN INTERLINGUA

### Observationes in Re le Nivellos Lipidic del Sero in Subjectos Rheumatic e Lor Fraternos

Esseva executate duo investigationes per medio de differente methodos chimic pro determinar (a) si quiescente subjectos rheumatic differe in le nivellos lipidic del sero ab lor fraternos non-rheumatic e (b) si le supplementation del dieta per alcoholo-solubile materiales de vitello de ovo modifica le nivellos lipidic del sero.

Esseva constatate que le nivellos lipidic del sero de quiescente subjectos rheumatic esseva plus basse que illos de non-rheumatic fraternos de circa le mesme etate. In le caso de cholesterol e de lipido total le differentia esseva statisticamente significative.

Le supplementation del dieta per alcoholo-solubile materiales de vitello de ovo esseva sequite per augmentos del nivellos lipidic del sero. Il pareva que iste augmentos attingeva un maximo intra 3 menses. Tamen, mesmo post 6 menses de dietas supplementate, le valores in le juveniles rheumatic remaneva infra le valores in lor non-rheumatic fraternos qui recipeva le dieta del familia sin supplementation.

Es discutite le possibilitate que susceptibilitate rheumatic es associate con un anormalitate del metabolismo lipidic.

# OBSERVATIONS OF CHLORPROMAZINE INDUCED JAUNDICE WITH CONTINUED USE OF THE DRUG

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Many cases of jaundice due to chlorpromazine have been observed and documented. In all such instances, the drug was discontinued during the period of jaundice, with evidences of improvement resulting from supportive therapy. The medical literature contains no reports of the course of patients, continued on the drug, despite the presence of jaundice. Redeker and Balfour[9] reported one case in which one injection of 25 mg. of chlorpromazine (Thorazine), was given intramuscularly, for nausea, in a jaundiced patient. This patient was said to have had no ill effects from the injected drug. Pollack[8] described patients who were continued on therapy without evidence of untoward effects. This report, however, gave no laboratory data or liver biopsy information.

We have observed 2 cases of jaundice during chlorpromazine therapy while the drug was inadvertently continued. The absence of similar reports in the literature, the nondeleterious result of such procedure, and the resulting implications, make these cases interesting, medically significant, and, we believe, worthy of reporting.

**Case Reports.** case 1. A 56-year-old male was admitted to Nazareth Hospital because of jaundice. It was stated that he enjoyed good health until November, 1954. He then began to complain of anorexia and nervousness, which was attributed to emotional reaction to his wife's death. One month prior to hospital admission, he was examined by a neurologist who placed him on Thorazine therapy. For the 4 pre-admission weeks he took 50 mg. of the drug four times daily. His nervousness subsided but the anorexia was supplemented by nausea. After 2 weeks of Thorazine therapy, his skin and sclerae became icteric and the excretion of dark urine and clay-colored stools was reported. After 2 weeks of progressive, painless jaundice associated with weakness and weight loss, the patient was hospitalized. The past medical history was negative except for the history of having had psoriasis for 30 years. The patient consumed one to two quarts of beer daily for many years.

Physical examination disclosed an obese, jaundiced and obviously nervous male in no acute distress. In addition to the jaundice, the skin showed many lesions typical of psoriasis. Sclerae were icteric. The physical examination was otherwise negative. Routine urinalysis, blood count, sedimentation rate, serology, blood urea nitrogen, heterophile antibody and clot retraction time determinations were normal. A glucose tolerance test showed a diabetic curve. Cephalin flocculation was negative in 48 hours and the thymol turbidity was 2 units. Gastric analysis revealed no free HCl before or after histamine injection. The stool guaiac test was negative. Other hepatic function tests are tabulated in Table 1.

Chest roentgenogram demonstrated mild cardiac enlargement. An upper gastrointestinal Roentgen study disclosed an area in the prepyloric region that could not be defi-

nitively interpreted by the roentgenologist. He regarded it as an area of gastritis but could not rule out the possibility of an infiltrating tumor. Cholecystogram showed a functioning gallbladder, with normal dye concentration but impaired response to fatty foods. A Roentgen-ray study after barium enema was negative. The electrocardiogram revealed a sinus bradycardia.

presumed to be bile, secondary to biliary stasis. In the portal spaces, aggregations of inflammatory cells, chiefly lymphocytes are noted. The hepatic cells are indistinct and show large globules of fat dispersed, intermittently, and displacing the cytoplasm of the cells. This is severe fatty dystrophy. The biliary stasis is compatible with chlorpromazine jaundice.

TABLE 1.—HEPATIC FUNCTION TESTS IN CASE 1.

| Dates | 2/13/55 | 2/27 | 3/12 | 3/19 | 3/21 | 3/23 | 3/28/55 | 4/4 |
|---|---|---|---|---|---|---|---|---|
| Thorazine | ********** | | | _____ | ********** | | | |
| Alkaline Phosphatase | | | 12.8 | | – | | 9.2 | – |
| Cholesterol | | | 190 | | – | | – | |
| Van den Bergh | | | | | | | | |
| Direct | | | immed. | | del. | | del. | |
| Indirect | | | 2.3 | | 2.0 | | 0.2 | |
| Jaundice | | | ********** | | ********** | 3/23 | | |

(Patient receiving 50 mg. Thorazine, q.i.d.)

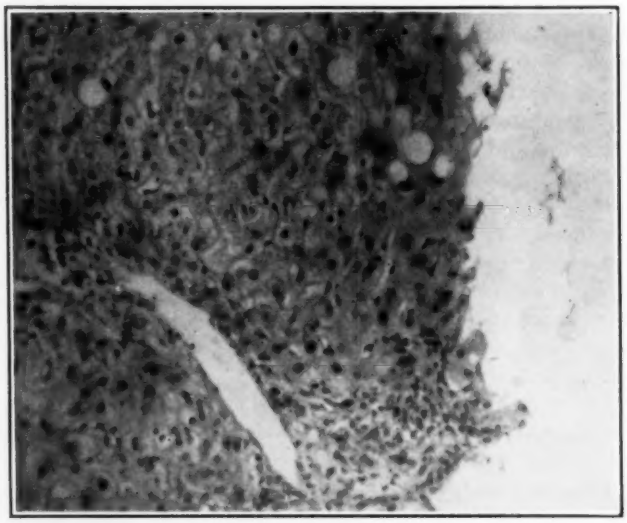

Fig. 1.—Case 1, illustrates biliary stasis and peri-portal inflammatory cells, chiefly lymphocytes. There is also evidence of fatty dystrophy.

During the course of studies, there developed a single, small, movable, nontender node in the right axilla. This was surgically removed and after microscopic study, the pathologist reported it to be fatty tissue. Liver biopsy was performed and the pathologist reported as follows: There is greenish yellow pigment scattered irregularly. This is

The patient was admitted to the hospital on March 12 and from that date until March 19, during the course of studies, he had received no chlorpromazine. The drug was accidentally readministered on March 19, despite the patient's continued icteric state. On March 21, two days after restarting chlorpromazine therapy, the jaundice began to

abate and by March 23, it was clinically cleared.

It was agreed that the etiologic agent of the jaundice was chlorpromazine. This drug, however, was continued, and on the 5th of April, 14 days after the clinical disappearance of jaundice, the patient was subjected to laparotomy. This procedure was deemed advisable in view of the achlorhydria and the roentgenologist's interpretation of the stomach roentgenograms. The operative findings were normal and a biopsy of the stomach was microscopically normal. Unfortunately, biopsy of the liver was not done at this time. The patient made an uneventful recovery and was discharged from the hospital on April 16. At this writing, 18 months later, the patient is well and has had no recurrence of jaundice. Chlorpromazine therapy was not continued after discharge from the hospital.

for bile; total proteins were 6 gm., with albumin 2.7 gm. and globulin 3.3 gm. Thymol turbidity was 10 units and the cephalin flocculation was 4 plus in 48 hours. Prothrombin time was 62%. Results of other liver function studies are tabulated in Table 2.

Chest and abdominal Roentgen studies were negative. An electrocardiogram showed left ventricular hypertrophy and strain pattern. The first report of two liver biopsies showed no evidence of inflammatory reaction, only a slight increase in pigment in the canalicular areas.

After 24 hours of parenteral therapy of 5% glucose, Thorazine, 25 mg., q.i.d. was accidentally administered, besides a high caloric carbohydrate, protein and vitamin diet. On the eleventh day, jaundice began to disappear. The second liver biopsy revealed considerable deposition of brown granular pig-

TABLE 2.—HEPATIC FUNCTION TESTS IN CASE 2.

| Dates | 1/2/56 | 2/1 | 2/4 | 2/6 | 2/8 | 2/10 | 2/13 | 2/17 | 2/20/56 |
|---|---|---|---|---|---|---|---|---|---|
| Thorazine | | | ********** | ********** | ********** | ********** | ********** | ********** | |
| Phosphorus | | | 3.2 | 3.6 | 3.8 | 4.0 | 4.4 | 3.8 | |
| Alkaline Phosphatase | | | 4.0 | 7.6 | 9.0 | 8.6 | 10.0 | 4.8 | |
| Cholesterol | | | 480 | – | – | – | – | 360 | |
| Van den Bergh | | | | | | | | | |
| Direct | | | immed. | | | immed. | | immed. | |
| Indirect | | | 5.4 | 2.8 | 2.6 | 2.6 | 1.2 | 1.3 | |
| Jaundice | | | ********** | ********** | ********** | ********** | 2/13 | | |

(Patient receiving 25 mg. Thorazine, q.i.d.)

CASE 2. A 68-year-old male was admitted on February 3, 1956, because of jaundice. He had a prior admission, on December 22, 1955, because of a cerebrovascular accident, complicating the course of arteriolar hypertension. During his first admission, he was placed on Thorazine, 25 mg. q.i.d., to control anxiety and mental agitation. Four days prior to the second admission, he complained of anorexia, nausea and vomiting and was observed to be icteric. The urine was very dark, and the stools, clay-colored.

Physical examination, on second admission, disclosed a well-nourished, icteric male, complaining of nausea and vomiting. The blood pressure was 170/130. Skin and sclerae were icteric. The heart was slightly enlarged to the left. The lung fields were clear. The liver was palpable 3 cm. below the costal border and tender. There was motor paralysis of the right arm and leg, from the previous cerebrovascular accident. Significant laboratory findings were that the urine was positive

ment. The individual cells were microscopically somewhat indistinct. In the portal spaces there were aggregations of inflammatory cells. The patient was discharged clinically improved and continued on the same dosage of Thorazine for 4 months, with no recurrence of jaundice.

**Discussion.** The symptom complex of chlorpromazine-induced jaundice is similar to that of extrahepatic jaundice. The icteric phase may be preceded by anorexia, nausea and, on occasion, vomiting. The jaundice may appear as early as 9 days (Hollister *et al.*[2]) or as late as 5 weeks[10] after institution of drug therapy. The duration of icterus has been reported to vary from 48 hours to 3 months (Huizenga[3]). The drug dosage is not related to the ap-

pearance of jaundice (Cohen and Archer[1], Kinross-Wright[5], Kurland[6] and Litteral and Wilkinson[7]). After the icteric phase clears, readministration of the drug has produced a recurrence of jaundice, according to some authors (Hollister *et al.*[2], and Pollack[8]). The liver may enlarge but is usually nontender, although tenderness has been found in some cases

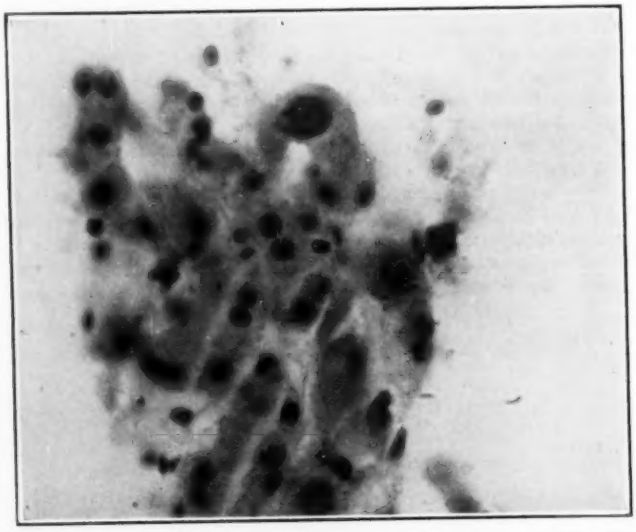

Fig. 2.—First liver biopsy of Case 2, demonstrates slight increase in pigment in the canalicular areas.

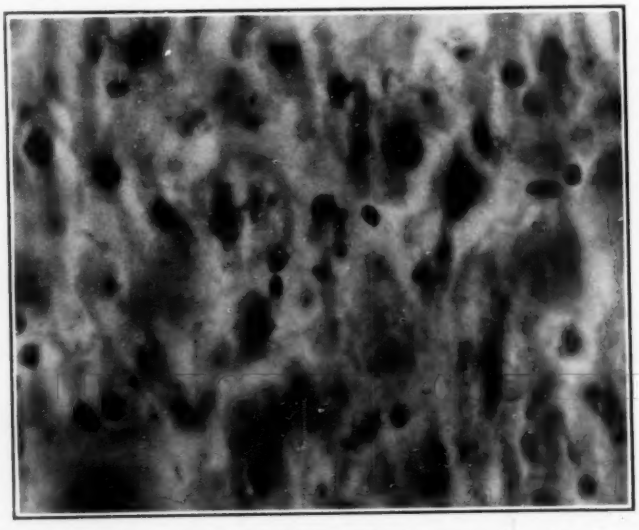

Fig. 3.—This second liver biopsy performed in Case 2, shows considerable deposition of brown granular pigment and periportal aggregations of inflammatory cells.

(Redeker and Balfour[9]). A mild eosinophilia may be present and there is an elevation of both serum bilirubin and cholesterol levels. Serum alkaline phosphatase is elevated and may remain so after the jaundice has cleared. The cephalin flocculation test is usually negative but may be positive (Hollister *et al.*[2], Johnson and Doenges[4], and Stein and Wright[11]).

In primary intrahepatic cholestasis due to chemical agents, as chlorpromazine, the pathogenesis is still obscure. The current thought resolves into several possible mechanisms. One is that of hypersensitivity to the drug. The other hypothesizes the removal of some essential metabolite from the liver, as a result of the drug action. The theory most acceptable to us is that injury or functional disturbance of the hepatic cells or cholangioles results in alteration of normal bile hydration, thus increasing the viscosity of bile.

The pathology of chlorpromazine-induced jaundice is similar to that of extrahepatic obstructive jaundice, and is referred to as primary intrahepatic cholestasis. It is reported to be likewise similar to the jaundice produced by methyl testosterone and viral agents (Johnson and Doenges[4]). The typical microscopic picture of chlorpromazine-induced jaundice consists of marked pigmentation of the central hepatic cells and neighboring Kupffer cells. Two types of pigment have been described, namely, a brown amorphous pigment and a yellowish brown granular material (Stein and Wright[11]). The intracellular canaliculi are distended by bile and there is plugging of the bile capillaries by inspissated bile (Johnson and Doenges[4]). There may or may not be focal degenerative changes of the hepatic cells. In the portal triad area there is usually an infiltration of inflammatory cells consisting of lymphocytes, mononuclear cells and, at times, neutrophilic or eosinophilic polymorphonuclear leukocytes. The architecture of the hepatic lobules and liver cords is preserved.

The 2 patients here reported received chlorpromazine and developed the clinical evidences of jaundice. The presence of the icteric state was confirmed by laboratory studies, and liver biopsy specimens were compatible with the usual pathologic picture of chlorpromazine-induced jaundice. Both these patients were continued on chlorpromazine despite the presence of jaundice. In Case 2, there was a one-day lapse of chlorpromazine therapy and in Case 1, the drug was discontinued for 8 days. Therapy, however, was accidentally reinstituted during the period of jaundice in each patient. In addition to the continued chlorpromazine therapy, each patient was given supportive therapy consisting of a high carbohydrate and protein, low-fat diet supplemented with vitamins.

The subject of Case 1 showed evidence of fatty dystrophy of the liver. This was attributed to the patient's alcoholic intake and not related to the chlorpromazine therapy.

Despite the reinstitution and continued therapy with the causative drug agent, the jaundice disappeared as readily and completely, without recurrence, as would be expected with drug withdrawal.

**Comment and Summary.** Two cases of chlorpromazine-induced jaundice were continued inadvertently on the causative chemical agent without evidence of untoward effects. The clinical picture of jaundice cleared and did not recur, despite continued therapy. This observation, therefore, raises some question as to the necessity of discontinuing therapy because of the appearance of jaundice. The ability to continue chlorpromazine therapy, despite

the appearance of jaundice, would be of some selective therapeutic value, especially in neuropsychiatric patients. It is the opinion of the authors, that this procedure may be followed, only if the patient is hospitalized, and close clinical observation and laboratory facilities are available. The purpose of continuing therapy under such circumstances would be to supplement the present study and confirm these observations, the validity of which would enhance the scope and usefulness of a therapeutic agent.

Cortisone is known to have two effects on bile. One is hydrocholeresis or an increase in bile volume, and the other is choleresis or an increase in concentration of bilirubin and bile salts in the bile. A recent report (Stein and Wright[11]) cites the disappearance of chlorpromazine-induced jaundice after 2 days of cortisone therapy. It is interesting to speculate on the possibility of a temporary interference, or relative insufficiency of cortisone activity, at the hepatic cellular or cholangiolitic level, in the patients who develop jaundice on chlorpromazine therapy.

We suggest that with strict control with hospitalization, such jaundiced patients might be cautiously continued on this therapy, since additional evidence is necessary to confirm these observations before recommending this practice.

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*(Interlingua on page 113)*

# PROGRESS
# OF
# MEDICAL SCIENCE

## MEDICINE

UNDER THE CHARGE OF

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## VIRUS MENINGITIS

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IN 1924 Wallgren[102] introduced the term "aseptic meningitis" to designate an epidemic disease he believed to be a nosologic and etiologic entity. To be included in this category, the following criteria had to be met:

1. An acute onset with signs and symptoms of meningeal irritation
2. Pleocytosis
3. Cerebrospinal fluid sterile by usual bacteriologic techniques
4. Comparatively short benign course without secondary complications
5. Absence of any indications of parameningeal disease (otitis, sinusitis, trauma, and others) or systemic infection which might have meningitis as a complication (tuberculosis, mumps, poliomyelitis, typhoid, leptospirosis, and others)
6. Absence in the community of epidemic disease that might be associated with meningitis

In the years that followed, it became increasingly clear that "aseptic" meningitis was not a specific disease but rather a syndrome associated with a large number of diseases. Some 27 years after his original paper on the subject, Wallgren[100] apparently concurred with this concept. As virologic techniques have been improved, a number of filterable agents have been found to be etiologically related to the syndrome he described. It is safe to say that none of these agents produces disease that consistently satisfies Wallgren's criteria. Thus, in an attempt to retain the usefulness of the term "aseptic meningitis," workers have gradually changed its meaning. When it became clear that many of the cases

grouped in this category represented complications of systemic infections, such as those caused by mumps, Coxsackie, poliovirus, and even lymphocytic choriomeningitis, Wallgren's fifth and sixth criteria were tacitly dropped. Because limitation of the designation exclusively to cases with a short benign course cut across etiologic boundaries, his fourth criterion has often been overlooked. Most workers now define "aseptic meningitis" as a syndrome characterized by the acute onset of signs and symptoms of meningeal irritation in the absence of any indications of parameningeal disease in which the spinal fluid is sterile by the usual bacteriologic techniques and has an abnormally increased cellular content, usually predominantly lymphocytic. In addition, there has arisen the vague, unstated, and somewhat paradoxic custom of discarding some cases with evident systemic involvement while retaining others. Thus, few have any misgivings in including instances of mumps meningitis and pancreatitis, of lymphocytic choriomeningitis and pneumonia, or of herpes simplex meningoencephalitis and oral lesions. For some reason, however, cases of scarlet fever, typhoid fever and pneumococcic pneumonia, complicated by sterile, nonsuppurative meningitis, are "obviously" to be excluded. We may include leptospiral meningitis but must discard syphilitic disease. There is, moreover, an attempt on the part of some to restrict the term "aseptic meningitis" to cases in which meningeal involvement is unaccompanied by the signs and symptoms of encephalitis, with some compromise necessary when such a restriction serves to cut across etiologic groupings.

The time appears to be at hand when the designation "aseptic meningitis," with all its vague and inconsistent connotations, should either be abandoned or defined more clearly. The term "lymphocytic meningitis," to include all affections accompanied by pleocytosis which is usually predominantly lymphocytic, would seem to be a far more useful generic term. Subdivision of the group can then be made on an etiologic basis (Table 1). In addition, there is need for a term to include all cases of lymphocytic meningitis in which an etiologic diagnosis based on clinical features cannot be made. It is in this sense, for want of a better designation, that the term "aseptic meningitis" will be used in this paper. It should be clear that no connotations of a viral or leptospiral etiology are implied. It is merely used in place of the more cumbersome term "lymphocytic meningitis of obscure etiology."

The causes of lymphocytic meningitis are so manifold that a full discussion of the problem is impossible within a single presentation of this type. Since the most rapid strides in our understanding of the viral meningitides have been made in the last two decades, with the consequent keen interest presently aroused by these advances, this review will be limited to this category. In a way, such emphasis on the viral etiology of lymphocytic meningitis is unfortunate. When a patient manifests lymphocytic meningitis, no competent house officer would fail to include viruses and leptospira in his differential diagnosis, and the more enthusiastic ones would not fail to obtain the proper materials for such studies. To some, unfortunately, the presence of lymphocytic pleocytosis is almost synonymous with a viral or leptospiral etiology. Few make an adequate investigation to exclude such causes as sulfonamide reaction, heavy metal toxicity, or even paranasal sinus disease. Perusal of Table 1 clearly indicates that viral and leptospiral infections constitute only a small part of the problem.

TABLE 1.—ETIOLOGY OF LYMPHOCYTIC PLEOCYTOSIS

A. *Noninfectious Factors*
  1. *Mechanical Irritation of Meninges*
    a) Drugs instilled into cerebrospinal fluid
    b) Abscesses and foci of infection neighboring meninges
    c) Spinal tap
    d) Intracranial hemorrhage
    e) Venous thromboses
  2. *Toxic Factors*
    a) Heavy metals, such as:
      (1) Arsenic
      (2) Lead
    b) "Toxic" meningitis associated with many bacterial infections, as for example:
      (1) Scarlet fever
      (2) Typhoid
      (3) Pertussis
      (4) Pneumococcic pneumonia
  3. *Neoplastic Disease*
    a) Tumors of the central nervous system
    b) Some lymphomas
  4. *"Allergic" Factors*
    a) Post-rabies vaccination
    b) Post-animal serum administration
    c) Post-toxoid immunization
    d) Sulfonamide drugs

B. *Infectious Factors*
  1. *Bacterial Meningitis*
    a) Suppurative meningitis partially treated, healing, or (rarely) early
    b) *Mycobacterium tuberculosis*
    c) *Listeria monocytogenes*
  2. *Mold and Yeast Infections*
    a) *Cryptococcus neoformans*
    b) *Candida albicans*
    c) *Coccidioides immitis*
    d) *Blastomyces*
  3. *Spirochetal Infections*
    a) *Treponema pallidum*
    b) *Leptospira*
  4. *Rickettsial Infections*
  5. *Protozoal Infections*
  6. *Helminthic Infections*
    a) *Trichinella spiralis*
  7. *Viral Infections*
    a) Poliomyelitis
    b) Mumps
    c) Coxsackie
    d) Enteric cytopathogenic human orphan viruses
    e) Herpes simplex
    f) Encephalomyocarditis
    g) Lymphocytic choriomeningitis
    h) Herpes zoster
    i) Arthropod-borne encephalitides
    j) Infectious hepatitis
    k) Lymphogranuloma venereum
  8. *Presumably Viral Infections*
    a) Primary atypical pneumonia
    b) Infectious mononucleosis
    c) Cat scratch disease

TABLE 1.—ETIOLOGY OF LYMPHOCYTIC PLEOCYTOSIS.—*(Continued)*

C. *Diseases of Unknown Etiology*
1. Multiple sclerosis
2. Periarteritis nodosa
3. Sarcoidosis
4. Neuromyelitis optica
5. Postinfectious encephalitides
   a) Measles
   b) German measles
   c) Smallpox
   d) Vaccinia
   e) Varicella
   f) Mumps
6. Acute hemorrhagic necrotizing encephalopathy

POLIOMYELITIS. Because poliomyelitis has been discussed so extensively in recent years, it will not be presented in detail here. An excellent review has been published recently under the auspices of the World Health Organization[19]. Several points, however, deserve emphasis.

Disregarding paralytic cases, the polioviruses are still, in all probability, the commonest cause of aseptic meningitis. The clinical features of nonparalytic poliomyelitis are all nonspecific, and accurate diagnosis by this means alone is not possible. It is true that the temporal and geographic relationship of some cases of aseptic meningitis to obvious paralytic poliomyelitis makes it more likely that the former represent instances of nonparalytic poliomyelitis. It is equally true, however, that epidemics of other viral diseases that produce a similar nonparalytic illness may, and frequently do, coexist with poliomyelitis in a community. Virologic and serologic investigations consistently confirm the diagnosis of poliomyelitis more frequently in cases of paralytic disease than in those classified as nonparalytic. We must conclude, therefore, that an accurate diagnosis of nonparalytic poliomyelitis can be made only by isolation of the virus from the feces, by demonstration of a rise in the titer of neutralizing or complement fixing antibodies, or by both these means. Despite their ease, serologic procedures have proved disappointing when used alone for the diagnosis of poliomyelitis, since a considerable proportion of patients have demonstrated their maximal antibody titer by the time they come to the attention of a physician.

MUMPS. Knowledge of neurologic involvement in mumps has existed for many years but was limited, by lack of a specific laboratory diagnostic test, to those cases that exhibited evident parotitis or, by inference, to cases epidemiologically related. In some instances the diagnosis has been inferred, in the absence of parotitis, by circumstantial evidence of appearance of parotitis in contacts after a proper incubation period[24,51,101]. When it was shown by Habel[38] and by Levens and Enders[71] that the mumps virus could be cultivated in the chick embryo and that it could be detected by its property of agglutinating red cells, it was quickly demonstrated that the agent could be isolated from the spinal fluid of patients with mumps meningitis[40]. Although a number of such reports followed[65,81], it became evident that isolation of the agent from the cerebrospinal fluid was irregular and the diagnosis would not be made in a significant proportion of cases by this technique

alone. Introduction of hemagglutination inhibition[81] and complement fixation[26] tests made it possible to study mumps infections by relatively simple serologic techniques.

In order to understand the role of mumps virus infections in the syndrome of aseptic meningitis, we need the following information: a) the frequency with which meningitis occurs as a complication of parotitis, b) the relative incidence of meningitis as the only obvious feature of mumps infection, and, finally, c) the importance of mumps as a cause of aseptic meningitis.

Afzelius-Alm[2], in summarizing a number of studies, concluded that about 55% of patients with mumps parotitis have pleocytosis. Of those with pleocytosis, about half have signs and symptoms of meningeal irritation ("manifest" meningitis), whereas the other half do not ("latent" meningitis)[5]. Although the data are too sparse to permit any conclusions, it is interesting that in three studies of mumps patients of all ages, 280 of 446 patients (63%) were found to have meningitis, while in three studies involving members of the U.S. Armed Forces (presumably all adults), only 88 of 215 (41%) were so affected. It is possible that meningitis is more frequently associated with mumps infections during childhood. Furthermore, the frequency of meningeal involvement may vary from epidemic to epidemic as a result of variations in the neurotropic properties of the viral strains.

The incidence of mumps meningitis without clinical evidence of other organ involvement has not been determined accurately; estimates have varied from 5 to 30% of all mumps infections. Eberlein[24], who compiled the data from 24 different series, arrived at an estimate of 13%. In New England, a number of clinicians have had the impression that mumps meningitis without parotitis seemed to occur more frequently during the summer months[65]. The increased frequency of the diagnosis during the poliomyelitis season may, however, be a function of a higher index of suspicion of meningeal disease at such a time, rather than a true seasonal fluctuation.

Mumps is undoubtedly one of the important causes of aseptic meningitis. Adair and associates[1], in a study of 819 cases for which material was submitted to the Army Medical Services Graduate School, made a definitive diagnosis of mumps by complement fixation tests in 7.8% and a presumptive diagnosis in an additional 6.3% for a total of 14.1%. Afzelius-Alm[2] found an incidence of 8% among 76 similar cases in Scandinavia, whereas 15% of 45 cases studied in Louisiana[35] were attributable to mumps. In a small but interesting study of 17 cases of "nonparalytic poliomyelitis" collected during a summer season in New England when the reported cases of poliomyelitis showed a particularly low frequency of paralysis, Kilham and co-workers[66] found 6 (35%) to be mumps. In contrast, by serologic study of 75 cases of "polio-like disease" (excluding poliomyelitis) collected in one year in Louisiana, it was possible to detect mumps viral infections in only 7 (9%)[29]. It may be concluded that mumps is a cause of approximately 10% of all cases of lymphocytic meningitis of obscure etiology, the exact rate varying with the season, locale and year.

When mumps meningitis is unaccompanied by clinically detectable involvement of other organs, lack of definitive features precludes the proper diagnosis without the help of virologic or serologic techniques. A history of contact with a known case of mumps is helpful but only of presumptive value.

THE COXSACKIE GROUP OF VIRUSES. The

Coxsackie viruses were first described barely 10 years ago[17], but in this short span of time a tremendous amount of information has accumulated regarding these agents and the illnesses they produce. Since several extensive reviews have appeared recently[15,16,20,34,47,78], only a brief summary of the general aspects of Coxsackie virus infections will serve our purpose.

The Coxsackie viruses are truly world-wide in distribution, having been found on all six continents and in practically all latitudes[78]. Most isolations can be made in the summer and fall. Man appears to be the primary natural host, and dissemination of the agents apparently occurs primarily by human contact with the feces of infected persons, either directly or by way of coprophagous flies or sewage[76]. Although human infection is exceedingly common, especially in childhood, manifestations of disease, as with poliovirus, probably occur in only a small proportion. In the infected individual, the richest source of Coxsackie virus is the feces, from which it may be isolated for weeks. It may be found in the throat for short periods of time and, rarely, in the blood. Occasionally, it has been possible to demonstrate the agent in affected muscle.

There are presently known to be 24 distinct types of Coxsackie viruses, as categorized by their ability to cause disease in suckling mice but not ordinarily in adult mice. These are divisible into two groups, designated A and B, by the nature of the disease and pathologic changes they induce in suckling mice. By this means 19 types are included in Group A and 5 in Group B[16]. Unfortunately, only 6 types regularly produce cytopathogenic changes in monkey kidney tissue cultures, including $A_9$ and all 5 types of Group B. Thus, the monkey kidney tissue culture technique is suitable for the study of human infections only with these particular types of Coxsackie viruses, and the more cumbersome and time-consuming method of suckling mouse inoculation is necessary for detection of the others. Neutralizing antibodies developed in response to infection are largely type-specific, and no common complement fixing antigen is shared by the group. For this reason, it is virtually impossible to make extensive use of serologic procedures for the diagnosis of human infections, since it would require substantial volumes of acute and convalescent blood and considerable labor to perform complement fixing studies against 24 Coxsackie antigens and even more to do neutralization tests in suckling mice. Diagnosis of Coxsackie infections, for all practical purposes, therefore, hinges on viral isolation with confirmation by serologic studies for the homologous type only.

Although information has accumulated rapidly with reference to human infections with Coxsackie viruses, reasonably conclusive evidence of their relationship to specific disease entities has been more difficult to obtain. The ubiquity of these agents and the frequency with which they may be isolated from the stools of asymptomatic individuals make it difficult to exclude the possibility that a silent Coxsackie virus infection may coexist with some other agent in a person with a given disease[47]. Indeed, the Coxsackie viruses were first isolated from 2 patients with paralytic poliomyelitis[17] and evidently represented a chance concurrent infection. Despite these difficulties, the Coxsackie viruses have been implicated unequivocally as a cause of herpangina[48], pleurodynia (Bornholm disease)[12,53,108], neonatal myocarditis[50,62] and lymphocytic meningitis[87].

Two methods have yielded convincing information on the etiologic rela-

tion of Coxsackie viral infections to aseptic meningitis. First, isolation of the agent from the spinal fluid or neural tissues of the diseased individual is strong evidence that the agent is the cause of the syndrome. Secondly, if infections with Coxsackie virus are demonstrated to be significantly more frequent in patients with lymphocytic meningitis than in a suitably constituted control group, one may infer that a causal relationship exists.

More than 20 years ago, Lindberg[72] described an apparent association between the occurrence of cases of aseptic meningitis and Bornholm disease. Somewhat later, Gsell and associates[37] reported a similar concurrence in Switzerland. In an epidemic of pleurodynia in the Red Hook section of Brooklyn during the summer, pleocytosis and clinical evidence of meningoencephalitis were demonstrated in 2 of the 18 children and 3 of the 22 adults hospitalized[44].

Thus, when the relation between Coxsackie viruses of the B Group and pleurodynia was described, it seemed probable that these agents would prove to be a cause of lymphocytic meningitis. Although investigations followed that demonstrated fecal excretion of Group B agents by some patients with aseptic meningitis, they were not considered convincing for the reasons discussed previously. Greater weight was given to reports of accidental infections with Coxsackie Group B viruses in laboratory workers in whom meningitis developed[54,88]. It was not, however, until Group B viruses were recovered from the cerebrospinal fluid of patients with lymphocytic meningitis[23,33,49] and from the spinal cord of a newborn child who died[61] that the etiologic association was established beyond reasonable doubt.

The relationship of Group A Coxsackie viruses to lymphocytic meningitis is much less clearly defined. Although one investigator claimed successful isolation of several Group A strains from the spinal fluid of such patients as long as 7 years ago[45], this report could not be fully accepted, in view of the fact that the author described evidence consistent with the possibility of laboratory contamination. Pohjanpelto[78] reported the isolation of 7 Group A strains from the feces of 110 patients with a diagnosis of meningitis or encephalitis, compared with detection of similar infections in 3 of a group of 268 control subjects. Although the difference was claimed to be statistically significant, insufficient information was presented for evaluation of the adequacy of the control group. In a 4-year study, Johnsson[52] demonstrated Group A Coxsackie infections in 6.2% of children with aseptic meningitis as compared to an incidence of 0.8% in those with paralytic poliomyelitis. In view of the possibility that a concomitant poliovirus infection might inhibit fecal excretion of Coxsackie virus, the use of patients with poliomyelitis as a control group is not fully convincing. In a recent study of 125 patients who suffered from a variety of "virus-like" illnesses, 30 of whom had a diagnosis of aseptic meningitis, Group A Coxsackie viruses were isolated from 4 of the 30 (13%) and from none of the others[63]. Although the majority of the patients were adults, a harsh control group was constituted during the season yielding 3 of the 4 isolations consisting of a study of 58 pediatric admissions to a contagious ward. Two Coxsackie Group A viruses were isolated (3.5%), both in children with a clinical picture consistent with herpangina. Interestingly, one of these strains was typed as $A_4$, while those isolated from patients with meningitis and encephalitis were $A_7$, $A_8$, and $A_9$. Moreover, monkey kidney tissue cultures failed

to reveal other agents, and serologic tests for mumps, eastern equine encephalitis, lymphocytic choriomeningitis, herpes simplex, leptospira and poliomyelitis all yielded negative results.

Recently, Gear and his co-workers[6,34] in South Africa reported the isolation of Group A Coxsackie viruses from the cerebrospinal fluid of 6 patients with meningoencephalitis. If this work is confirmed, there will be little reason to doubt that Coxsackie A viruses can cause lymphocytic meningitis.

THE ECHO GROUP OF VIRUSES. Widespread application of the tissue culture technique to the study of viruses recoverable from human feces has yielded a number of hitherto unknown agents. Because their pathogenic capacity for man was undetermined, they have been classified as enteric cytopathogenic human orphan viruses (ECHO)[11]. Sixteen agents have thus far been included in this group[75]. Although these agents have been isolated frequently from man, until recently evidence of their relationship to human disease has been scanty.

In 1955, Karzon and associates[59] studied a summer epidemic of "nonparalytic poliomyelitis" in Holland, N.Y., involving 24 persons from 16 households. All 7 of the hospitalized patients, as well as several of their familial associates, were shown to have an ECHO Type 6 viral infection. In the same communication, the authors described briefly the isolation of ten orphan agents from the cerebrospinal fluid of patients who became ill during a concurrent generalized outbreak of aseptic meningitis, 7 of which were ECHO Type 6 virus. Duncan and co-workers[23] have isolated 2 as yet unidentified orphan viruses from the spinal fluid of similar patients in Canada, and an agent isolated from the spinal cord of a child who died of bulbospinal polio-like disease some years ago[95] has recently been found to be a Type 2 ECHO virus[59]. It appears that an outbreak of polio-like disease associated with ECHO virus Type 6 infections occurred over a wide area in the northeastern part of the United States during 1955, as evidenced by reports from western New York State[112], Massachusetts[62], and Connecticut[18].

Winkelstein and associates[112] have presented extremely interesting preliminary data on the epidemic they observed in Erie County, N.Y. Of 156 patients with nonparalytic polio-like disease investigated, 68% presented evidence of excretion of ECHO virus, whereas only 4% excreted poliovirus. None of the 31 patients with paralytic disease excreted ECHO 6, while 68% yielded polioviruses. When isolations were charted temporally, those of ECHO 6 virus were seen to parallel the epidemic curve of nonparalytic polio-like disease, whereas poliovirus isolations paralleled the incidence of paralytic cases. Fecal excretion of this agent was demonstrable in 14 of the 28 (50%) febrile contacts of cases of ECHO 6 meningitis, as contrasted with only 9 of the 58 (16%) apparently healthy contacts. Recently, Wenner[110] has described an outbreak of what appears to have been ECHO Type 4 meningitis in Marshalltown, Iowa.

In view of this recent information emanating from several sources, there is little doubt of the etiologic relationship between some of the ECHO viruses and the syndrome of aseptic meningitis. The frequency with which these viruses cause polio-like disease, particularly in nonepidemic circumstances, is as yet undetermined. It seems probable, however, that this group of agents, together with the polioviruses, mumps and the Coxsackie

group, will prove to be among the four most important causes of aseptic meningitis.

LYMPHOCYTIC CHORIOMENINGITIS. When Armstrong and Lillie[4] identified a new viral agent, which they named lymphocytic choriomeningitis (LCM), and it was shown to be capable of infecting humans[70,80], it was widely believed that the etiology of Wallgren's syndrome of "aseptic meningitis" had been elucidated. Indeed, the "Standard Nomenclature of Disease"[55] listed acute aseptic meningitis and LCM as synonyms, a source of confusion as late as 1942.

The general features of LCM infections have been reviewed adequately elsewhere[3,27] and will only be covered briefly here. The natural host of LCM appears to be the mouse, from which it may be isolated without reference to obvious illness. Infected gray and house mice eliminate the agent in nasal secretions, semen, urine and feces, and it has been suggested that the dust resulting from the drying of these products may be effective in transmitting the disease to man. In any case, human infections are frequently noted in the absence of a history of known direct contact with mice. The agent may be maintained indefinitely in this host by transmission from mothers to their young. Although LCM virus has also been found to be harbored naturally in guinea pigs, monkeys, and dogs, the importance of these animals in the epidemiology of human disease is unknown.

In a series of 2,000 randomly collected sera from persons in the United States, 11% were shown to possess neutralizing antibody to the LCM virus. If this is an accurate index of the frequency of human infections with this agent, it may be inferred that obvious meningeal involvement develops in only a small proportion of people who are infected. Epidemiologic investigations of known cases of LCM meningitis have revealed that household associates may have suffered (a) an inapparent infection or (b) a grippal syndrome characterized by abrupt onset and a duration of 2 to 10 days. About 35% of those with meningeal involvement had a history of a grippal syndrome occurring about 7 to 10 days previously[1]. Rarely, LCM virus may be the cause of viral pneumonia[91], encephalitis, and encephalomyelitis with paralysis[10,28,74] or death[10,91].

The diagnosis of LCM infections can be made by isolation of the agent from the blood and spinal fluid, occasionally from urine and nasal secretions and, rarely, from a variety of organs in a fatal case. Serologic evidence of infection can be had by the appearance of complement fixing or neutralizing antibody in convalescence. Neutralizing antibody does not usually appear for 6 to 10 weeks after the onset of symptoms and persists for years; complement fixing antibody, on the other hand, appears earlier and is present for a shorter period of time. Diagnosis of LCM infections is not possible by clinical features alone.

Various studies prior to 1952 indicated that a significant fraction of cases of lymphocytic meningitis was caused by LCM viral infection. Smadel[92] made this diagnosis in 25 (15%) of a total of 165 cases collected in New York, whereas Rasmussen[79] found 32 (8.5%) in 374 cases among U.S. Army personnel. In a later study of a similar group at the Army Medical Service Graduate School[1], 8.1% of 454 cases were shown to be associated with LCM infection.

On the other hand, studies in Scandinavia have failed to reveal any significant incidence of meningitis attributable to LCM[2,31]. A study of 58 cases in Louisiana collected over a 3-

year period revealed only two such infections[35], and investigation failed to reveal a single case among 75 instances of nonpoliomyelitic, polio-like illness collected during 1956[29]. It seems probable that meningeal disease associated with LCM infections varies greatly in frequency from area to area. Certainly, it has been rare in Canada and the southeastern part of the United States by comparison to its prevalence in the Washington, Philadelphia, New York and Boston areas[83]. There is little doubt that it accounts for only a small number of the cases of aseptic meningitis in any area studied thus far.

HERPES SIMPLEX. Although it has been almost 40 years since herpes simplex virus was isolated from "fever blisters"[36,73], the recognition that this agent may cause widespread pathologic changes in the human host is of relatively recent vintage. Central nervous system involvement was noted with primary herpes simplex infections in man about 10 years ago[94,111,114] but was believed to be universally fatal. In the past 7 years, there has been increasing recognition that primary herpes simplex infections may be followed by nonfatal meningoencephalitis or even benign lymphocytic meningitis. In a study of 65 such cases, Afzelius-Alm[2] found serologic evidence of a primary herpetic infection in 13 (20%), while Adair and associates[1] found only 6 among 114 cases (5.3%). Of a total of 150 cases studied in Louisiana during the past 3 years, only 3 (2%) primary herpes simplex infections could be demonstrated[29,35].

There are no sufficiently distinctive features to make diagnosis possible by clinical examination alone. Isolation of the agent from spinal fluid (or neural tissues in necropsied cases) is possible by inoculation of embryonated chick eggs[86], suckling mice[64], rabbits[36,73], or tissue cultures[84]. However, viral isolation from the spinal fluid is probably unsuccessful often enough to render this procedure alone inadequate for diagnostic investigation. Until recently, complement fixation tests for herpes simplex were complicated by the difficulty of preparing adequate antigens from the fluids or membranes of infected chick embryos. Consistently more potent antigens can now be obtained simply from infected HeLa and KB cell tissue cultures. In addition, neutralizing antibody titers of acute and convalescent sera are relatively easily determined in tissue cultures.

ENCEPHALOMYOCARDITIS. Encephalomyocarditis virus thus far has had an unfortunately confusing history. First isolated from wild cotton rats in whom the Yale-SK strain of poliovirus was being passaged[57], it was given the name Columbia-SK virus and was believed to be a murine variant of poliovirus. Soon thereafter, another strain was isolated from the brain of hamsters in which extracts of brain and spinal cord were being passed from a patient who died of an undiagnosed paralytic disease; it was given the name MM. In 1945, Helwig and Schmidt[41,85] isolated an agent from a captive chimpanzee that died of myocarditis in Florida; this they designated as encephalomyocarditis (EMC) because of its propensity for these tissues in experimental animals. Some years later, it was shown to be immunologically identical with the Col-SK and MM strains[105]. Meanwhile, a similar agent was isolated from a captive rhesus monkey at Entebbe, Uganda, and was termed Mengo encephalomyelitis virus. The Col-SK, MM, EMC and Mengo viruses are identical by all presently available techniques of immunologic analysis, differing only in their source of origin[22,105]. The diversity of terms used in the medical literature is a source of confusion to all but the expert. It

would be well if the designation encephalomyocarditis were to be adopted universally.

Great interest centers on this agent because of its demonstrated ability to produce severe encephalomyelitis and myocarditis in primates, with the obvious possibility of its pathogenicity for man. The subject has recently been reviewed by Gajdusek[30]. Epidemiologic information on EMC virus infections is fragmentary. The agent is worldwide in distribution, having been found in North America, Africa, the Philippines[93], Germany, Sweden and Holland[97]. It has been isolated in nature from the cotton rat, hamster, mongoose, squirrel and mosquito, whereas monkey, man and several species of wild rats have been shown to possess specific antibodies[67,103]. A serologic survey of wild rats collected from various regions of the United States and Canada[104] has demonstrated that an appreciable number possess neutralizing antibodies to EMC virus, with wide variation from region to region, while simultaneous study of a variety of other rodents failed to reveal any evidence of infection.

Evidence of disease produced by EMC viral infection in man is sparse. In 1947 Smadel and Warren[93] demonstrated an increase of neutralizing antibody in paired sera from patients involved in an epidemic of a "3-day fever" among U.S. Army troops in the Philippines. The illness was characterized by a high fever of 2 to 3 days' duration, pharyngitis, signs and symptoms of meningeal irritation and lymphocytic pleocytosis. Dick and associates[21] succeeded in isolating the virus from the blood of a laboratory worker (Dr. Dick himself) who contracted encephalitis and demonstrated the presence of neutralizing antibody in the patient's serum during convalescence. Recently, there have been several claims of isolations of EMC virus from the blood, cerebrospinal fluid and stools of persons suffering from illnesses such as aseptic meningitis, encephalomyelitis, Guillain-Barré syndrome and myocarditis[7,9,68,98,99]. Particular attention must be given to the findings of Verlinde and van Tongeren, who isolated EMC virus from 3 of several hundred patients studied with disease of the central nervous system. All 3 were young children who suffered from a nonfatal illness diagnosed, respectively, as aseptic meningitis, paralytic poliomyelitis and encephalomyelitis. The agent was isolated from the stools of all 3 and from the throat of one. Neutralizing antibody studies of 2 of these children revealed a significant rise. Great care was taken to rule out the possibility that unknown laboratory animal infection could have resulted in spurious results by the use of a) both monkeys and mice, b) uninoculated controls and c) a successful re-isolation. Thus there seems little reason to doubt the occurrence of EMC infections in man.

When, however, uncontrolled studies of a number of cases of any syndrome yield evidence of infection with a given agent in a few of them, there is always the possibility that the agent actually has no etiologic relation to the syndrome. Thus, the isolation of an adenovirus from the pharynx of some patients with lymphocytic meningitis and the demonstration of a rise in homologous antibody titer does not necessarily indicate that adenovirus infection caused the meningitis. It is, therefore, of interest to note that three separate studies[32,56,60] have revealed that 12.4 to 16% of cases of lymphocytic meningitis possess hemagglutination-inhibiting antibody against EMC virus as compared with 0 to 3.7% in other diseases and 0.7 to 4.5% among healthy individuals. The demonstration

of a statistically significant increase in the frequency of this infection in cases of lymphocytic meningitis as compared to a suitable control population is strong evidence of a causal relationship between the syndrome and EMC viral infection.

We may conclude that all the evidence now available strongly suggests that human infection with EMC virus is not rare and that it may be the cause of a significant proportion of cases of aseptic meningitis. That it may also be a cause of acute myocarditis in man is an interesting speculation, in view of the pathogenic properties of this agent in other primates. This must remain in the realm of pure speculation, however, until verified instances of infection with this agent in such human cases are found.

THE ARTHROPOD-BORNE ENCEPHALITIDES. Extensive discussion of the arthropod-borne virus encephalitides is hardly necessary in this review. Only three of these agents are of importance as a cause of neurologic disease in the United States, namely, St. Louis, western equine and eastern equine encephalitis. Each of these has been largely a regional problem, St. Louis encephalitis occurring in mid- and southwestern United States and the distribution of the others have been obvious by their names. In recent years, however, evidence has been accumulated indicating a progressive spread of these agents to other areas. Eastern equine encephalitis is apparently a highly pathogenic agent for man, causing overt neurologic disease in most infected human hosts. Meningitis unaccompanied by evidence of encephalitis probably occurs rarely, and detection of such cases would be likely only in the midst of a sharp outbreak of human cases of encephalitis. The likelihood of its importance as a cause of aseptic meningitis, even in the regions in which it is localized, is negligible. The western and St. Louis viruses are much less pathogenic for man, and evidence exists that human infections may be followed by a) no signs of illness, b) an acute febrile disease without obvious involvement of the central nervous system, c) aseptic meningitis or d) frank meningoencephalitis. An excellent review of the arthropod-borne encephalitides has been written by Olitzky and Casals[77].

Human infections with Colorado tick fever, a fourth member of this group of viruses found in the United States, has thus far been limited to the Rocky Mountain region. Central nervous system involvement with this agent in man is probably rare[25].

MISCELLANEOUS VIRAL INFECTIONS. The presence of lymphocytic pleocytosis in many patients with herpes zoster has been known for many years and is not surprising in view of the demonstrated pathologic change in posterior root ganglia, peripheral nerves and the spinal cord itself[39,96]. Rarely, reports have purported to describe an abortive form of the disease in which cutaneous lesions appeared only as an erythematous patch, and it is possible that herpes zoster infections may involve the central nervous system without obvious skin or mucous membrane pathology. Until recently, however, it has been impossible to diagnose herpes zoster by other than clinical means, since the agent was not known to affect any experimental animal other than man, and no serologic procedures were available. Recently, Weller[107,109] succeeded in propagating an agent by inoculation of zoster vesicle fluid into cultures of human embryonic skin-muscle or foreskin and has presented evidence of antibody development by the fluorescent antibody technique. In addition, the preparation of a satisfactory com-

plement fixing antigen from infected tissue culture materials was successfully accomplished. We therefore have good reason to expect rapid accumulation of more information on infections with herpes zoster in the near future.

Involvement of the central nervous system in clinically typical cases of infectious hepatitis has been frequently recorded and is summarized in two relatively recent papers[69,106]. However, until either the virus of infectious hepatitis can be cultivated or specific serologic techniques for diagnosis become available, or both, it will be difficult to rule out the possibility of an error in diagnosis (for example, Weil's disease) or a coincidental infection with another agent. The occurrence of infectious hepatitis without obvious hepatic involvement has been suspected for years. It is possible, although purely speculative, that such cases may also be susceptible to neurologic involvement.

About 15 years ago, Sabin and Aring[82] described an instance of human meningoencephalitis in which multiple isolations of the virus of lymphogranuloma venereum from the spinal fluid left little doubt of the diagnosis, despite the absence of characteristic stigmata that might have suggested the nature of the etiologic agent. In view of the paucity of similar reports, however, it seems likely that the psittacosis-lymphogranuloma venereum group of agents is not a frequent cause of aseptic meningitis. Adair and coworkers[1] investigated 22 such patients but could find no evidence of infection with these viruses by complement fixation tests.

DISEASES OF PRESUMED VIRAL ETIOLOGY. Lymphocytic pleocytosis has been alleged to be a rare complication of primary atypical pneumonia, accompanying the clinical picture of meningitis, meningoencephalitis or myelitis[43,113], but the absence of any characteristic histopathologic lesions in fatal cases and the unavailability of any truly specific laboratory tests for diagnosis make it difficult to evaluate these claims. Of greater interest are reports of similar complications in infectious mononucleosis[8,46,58,90] in which the demonstration of atypical lymphocytes and heterophile antibodies in the cerebrospinal fluid[42,89] as well as evidence of lesions in the central nervous system of the rare fatal case analogous to those considered typical of the disease[13,14], leave little reason to doubt the accuracy of these observations. In all probability, however, aseptic meningitis is not frequently associated with infectious mononucleosis. Heterophile antibody tests of paired sera from 70 persons in Louisiana yielded no positive results[35], nor did 13 cases tested by Adair and associates[1].

It should be obvious, from the foregoing discussion, that a great deal has been learned in recent years about the causes of lymphocytic meningitis. The relationship of certain previously known agents to the syndrome has been more clearly defined, and the pathogenic potentialities of two newly discovered groups of viruses (Coxsackie and ECHO) have been elucidated. At long last, it is possible to say that the day is not far off when we will be able to put a specific diagnostic tag on the majority of cases which, in our ignorance, we have hitherto called "aseptic" meningitis.

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## NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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# NEUROPSYCHIATRIC-LIKE SYMPTOMATOLOGY OF ADDISON'S DISEASE: A REVIEW

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THE purpose of this paper is to focus upon those symptoms of Addison's disease which at times may be suggestive, at least superficially, of primary neurological or psychiatric disorders. Such symptoms tend to appear predominantly in those patients who have either been previously undiagnosed, inadequately treated with modern substitution therapy, or in those patients who are in an adrenal crisis or near-crisis from some stress. Stresses capable of producing adrenal crisis include excessive exposure to cold, infections, trauma, allergic reactions, and major or minor dental procedures, especially if the latter result in fasting or the loss of water[54].

**The Symptoms.** a) EASY FATIGABILITY AND PROGRESSIVE WEAKNESS (ASTHENIA). These are generally recognized as the commonest early clinical signs of crisis or relapse[2,5,7,11,17,20,26,28,31,41,44,45,52]. The asthenia may be intermittent and appear only under various stresses. Such patients may complain that they are "too tired to study" or even "too tired to vomit"[46]. Some may complain primarily of muscular fatigue on moderate exertion. Others experience weakness of such profound degree that they are virtually bedfast[36]. In many patients asthenia is manifested early and primarily as a feeling of inability to carry on the ordinary occupations. There may be an extreme degree of prostration in a well-nourished individual whose muscles feel firm and hard[27,33].

b) NAUSEA AND VOMITING. These symptoms are generally indicative of a relapse or an impending adrenal crisis[7,11,14,23,31,37,42,44,45,47]. Vomiting usually occurs much earlier in infants suffering from adrenocortical insufficiency than in adults, and tends to be projectile in nature[34,35,59].

c) ANOREXIA, WITH LOSS OF WEIGHT. Anorexia, with associated weight loss usually appears early, sometimes months or years before other clinical evidence of Addison's disease[7,11,23,28,31,35,42,44,52,55].

d) COLLAPSE AND SYNCOPE. Collapse and syncope are very common in untreated Addison's disease and are probably related to feeble cardiac action and low blood pressure[14,26,36,39]. In infants they are sometimes described by the parents as "sinking spells."

e) HICCOUGH. Hiccough is well known as a herald of impending crisis[12,27,41,47]. One author reported this alarming symptom present at one time or another in 43 of his 160 cases[42].

f) PAIN. Patients with Addison's disease often experience pain referable to the lumbar region, abdomen, precordium[5], back and thighs[20], epigastrium[39], head[33,37], knees, or plantar surfaces of the feet[27]. The pain is usually of a vague, dull, deep aching type. Pain in the back in particular may be an early and important symptom[16,33]. One writer states that 11 of his 160 cases of Addison's disease suffered from "pseudoperitonitis," in which the abdomen was hard and distended, with diffuse abdominal pain[42]. Another physician was so impressed with the symptom of pain in certain cases that he considered the "painful type" one of four distinct forms of Addison's disease, the other three being the "gastrointestinal," the "melanodermic," and the "asthenic."[5].

g) HYPOGLYCEMIC REACTIONS. The following are frequent terminal symptoms of an adrenal crisis and often appear to be at least partially due to hypoglycemia; tremors, tetany, convulsions, delirium, and wild maniacal frenzy[25,33]. Rarely, the picture of "pseudomeningitis" may appear, with transitory nuchal rigidity[45].

h) ANXIETY REACTIONS, WITH OR WITHOUT DEPRESSION. Either one or both of these reactions may at times dominate the clinical picture of Addison's disease. Common symptoms of anxiety are irritability, insomnia, restlessness and difficulty in concentration[3,9,10,11,12,26,37,44,56].

i) PSYCHOTIC REACTIONS. Although severe psychotic reactions are comparatively uncommon in Addison's disease, it is well to be aware of the fact that they may occur. Such reactions are usually not symptomatic of an impending or actual adrenal crisis. They may be of any degree and include various combinations of the following: seclusiveness[44], negativism[9,11], suspiciousness, impaired judgment, agitation, psychotic depression, delusions, hallucinations and bizarre posturing[37].

j) MISCELLANEOUS SIGNS AND SYMPTOMS. One clinician recently reported papilledema in a case of Addison's disease and cited two others from the literature[22]. Numbness and tingling in the extremities, and the sensation of oculonasal swelling have also been reported as occurring in Addison's disease[20]. Failing memory, mild transitory periods of confusion, loss of mental alertness and personality changes are all frequently associated with this disease[2,7,11,18,26,30,37,40,47].

**Differental Diagnosis of Addison's Disease.** The following are the major illnesses which may at times be confused with Addison's disease:

A) SO-CALLED "FUNCTIONAL ILLNESSES".

1) *Neurasthenic reactions.* Although the obsolete term "neurasthenia" actually referred to a symptom complex, it is still widely used and understood by the medical profession to apply to patients whose principal complaint is chronic fatigue[32,51]. One or more of the following are the usual precipitants of this type of reaction: Anxiety, repressed hostility, frustrations, disappointments, need for love, sexual dissatisfaction or conflicts, constant failure, and other family or social problems. Boredom, monotony and absence of goals may serve as contributory causes. The premorbid personality of the patient with this condition has usually been characterized by dissatisfaction and by a chronic sense of being thwarted and rejected. The premorbid characteristics often merge so insidiously into the symptoms of the reaction that it is difficult to determine its time of onset. It would appear that

the diffuse nervousness and sustained tension which result from deep-lying personal maladjustment and emotional conflicts produce a subjective sense of weakness and exhaustion in these patients. The course of the reaction is usually long, and unless properly treated psychotherapeutically the prognosis for symptomatic relief is poor[15,32].

Typically, these patients "drag around" on a low level of social adjustment, reacting to any increased physical or emotional effort or demand with palpitations, headaches, "sinking spells," and the like. Typically also, this fatigability is not associated with pleasurable activities, such as discussing their symptoms, going for rides, going to doctors, and others, but is selective in its nature, prohibiting the patient from carrying out gainful pursuits and unpleasant tasks. The patient pays exaggerated attention to the bodily organs and their functions. Gastrointestinal complaints are frequent. Other common symptoms include an excitability of the special senses (for example, intolerance of noise, bright lights, cold, and the like), symptoms of an associated anxiety state, vasomotor instability, impaired sexual potency, dysmenorrhea, paresthesias and hypesthesias. On awakening in the morning the patient feels exhausted. However, as the day progresses he feels better, and, in the evening, may be comparatively free from his sense of exhaustion. Apparent poor memory is due to preoccupation and lack of concentration. Most of these patients can be described by a combination of the following expressions: shy, awkward, irritable, lacking in confidence, indecisive, pessimistic, lacking in initiative and ambition, critical, whining, dissatisfied, envious, resentful, complaining, anxious, fault finding, and depressed. Patients with neurasthenic reactions will frequently have low blood pressure and a low basal metabolic rate. However, they are not pigmented. A definite history of recurrent anxiety episodes and the frequent presence of various conversion symptoms will suggest the proper diagnosis. Where there is doubt, the usual adrenal cortical function tests will generally serve to eliminate the presence of Addison's disease.

2) *Depression.* Chronic fatigue states are often depressions in disguise. At times patients with either depression or fatigue may phrase their complaints in terms of the other symptoms. This is more likely with the depressed patient, who may complain of fatigue. Cyclothymic patients are frequently unaware of their depressed affective state and complain only about their (apparent) mental and physical fatigue and exhaustion[24].

3) *Early schizophrenia.* A listless type of apathy and indifference to external circumstances is usually manifest. Sooner or later the physical complaints become obviously delusional.

B) NEUROSYPHILIS. Neurasthenic-like symptoms first manifested at middle age are suggestive of neurosyphilis[32].

C) BRUCELLOSIS (UNDULANT FEVER). "An essential feature of good treatment is the recognition and proper management of the post-infection syndrome of convalescent neurasthenia. In brucellosis lasting for several months, as in other chronic febrile states, there is a period after the activity of the infection is terminated when symptoms of weakness, easy fatigue, nervousness, mental depression, and loss of ambition may be prominent. The physician must recognize that these complaints do not necessarily reflect active infection. He must convey this information to the patient so that such reassurance will prevent the discouragement which often leads to a state of emotional disturbance lasting for many years"[50].

D) THIAMINE DEFICIENCY. Thiamine

deficiency may produce an asthenic reaction syndrome characterized by generalized feelings of weakness, fatigability, poor appetite, insomnia, various somatic complaints and subjective difficulties in concentration and memory[32].

E) MYASTHENIA GRAVIS. The characteristic feature in myasthenia gravis is the rapid fatigability of certain individual voluntary muscles or muscle groups. Early manifestations are usually ocular. In severe cases the exhaustion of the patient is seen by the fact that the lower jaw tends to drop down on the chest, and the eyes are kept open with difficulty. At times the characteristic "myasthenic smile" (almost a sneer) may be apparent. This facial expression is the result of deficient action on the part of the zygomatic and risorius muscles, and exemplifies the curious way in which, in this disease, some muscles are affected and others escape even when they derive their innervation from the same source. The gait is normal after rest, but as fatigue supervenes, it becomes shuffling, unsteady, and weak. The myasthenic electrical reaction and the therapeutic test with prostigmin are diagnostic[13,19,57].

F) SIMMONDS' DISEASE (post-puberal panhypopituitarism, hypophyseal cachexia, Simmonds' cachexia, pituitary cachexia). When anterior pituitary function is greatly reduced due to atrophy, tumor, infection, fibrosis, trauma or infarction with necrosis, the endocrine glands which it controls become insufficient. This leads to a complex syndrome whose cardinal findings are: Asthenia, low blood pressure, nervous and psychic disturbances, marked loss of weight often leading to cachectic emaciation, low basal metabolic rate, loss of sexual function, low excretion levels of follicle stimulating hormone, low or absent excretion of urinary 17-ketosteroids, and often a low blood sugar or a flat glucose tolerance curve[21]. Hypothermia, bradycardia, gastrointestinal disorders, anemia and achlorhydria may also appear[58]. Loss of body hair may be prominent[48]. Neuropsychiatric-like symptomatology may include apathy, poor memory, somnolence, and occasionally confusion, disorientation, severe depression alternating with excitement, hallucinations and delirium[49,57]. Sterility may be absolute. Intolerance to cold, reduction in sweating, premature senility, decay and loss of teeth and dry skin, may be present in any degree. The disease is about twice as common in females as in males, and appears most often between the ages of 20 and 60 years[49]. The asthenia is perhaps not as profound as in Addison's disease but is similarly unresponsive to rest. For some reason or other, patients with adrenal insufficiency secondary to panhypopituitarism, generally do not show increased pigmentation. Patients with panhypopituitarism are sensitive to any kind of medication[48]. These patients may be precipitated into actual crisis, for example, by the injudicious administration of thyroid extract or by the salt withdrawal test. The "water loading test" will often not distinguish between Simmonds' disease and Addison's disease. However, in the early stages of Simmonds' disease the administration of ACTH is followed by an increase in the urinary excretion of the neutral 17-ketosteroids and 11-oxygenated steroids, as well as a significant reduction in the blood eosinophil count and an improvement in the water loading test[49]. The Addisonian type of pigmentation does not often occur in Simmonds' cachexia, probably because aldosterone production is apparently not under the influence of the anterior pituitary[8,48].

G) ANOREXIA NERVOSA. This chronic condition occurs mainly in young women in the second and third dec-

ades of life. All of them manifest serious emotional disturbances[53]. There is no history of postpartum hemorrhage and no alterations in the sella turcica or other evidences of the existence of an intracranial neoplasm[49]. The symptoms are: a persistent lack of appetite (or disgust for food), extreme emaciation (often with a remarkable preservation of bodily vigor, at least in the early states of the illness, which may seem inconsistent with inanition due to constitutional disease), marked loss of weight, asthenia, amenorrhea, low basal metabolic rate, hypotension, dry scaly skin, low temperature, slow pulse and constipation. Vomiting is common if food is forced, and is often self-induced. Axillary and pubic hair are rarely lost. The amenorrhea usually begins before the patient has lost any considerable amount of weight.

Psychological studies on patients with anorexia nervosa reveal that these patients have serious neurotic traits, and sometimes even psychotic manifestations. There is usually a strong repudiation of sexuality, which is enhanced by their starved, emaciated, unattractive appearance. Some of the other personality characteristics often encountered are perfectionism, superior intelligence, introversion, stubbornness, selfishness, over-sensitivity, self-punitiveness, overconscientiousness, neatness, seclusiveness, shyness, and dependence upon others. Such patients generally give a history of poor relationships with their parents as well as difficulty in making friends[58]. The rejection of food is based on deep-seated emotional conflicts[51]. There is often a preceding history of obesity and overeating, with a feeling of shame at being fat. In some cases a pregnancy fantasy seems to have prompted the patient to start to diet. The illness brings a secondary but unconscious gain, in the form of desired attention, affection and sympathy from the family. Despite her pitiable plight the patient is often active or restless. Sustained effort is difficult. Death may occur from starvation after years of debility.

It is important to realize that in time, as these patients fail to eat and become extremely malnourished ,there is hypofunction of all the tissues of the body, including the pituitary gland, the thyroid, the adrenals and the gonads. In other words, a state of panhypopituitarism may eventually be superimposed upon a long-lasting case of severe anorexia nervosa. The main treatment is psychotherapy, but hormone medication is at times, at least partially successful, and may be given in order to stimulate the target glands or replace their hormones if the condition has persisted for a long time[48].

There may be a slight reduction in the serum sodium in this illness. Salt deprivation tests will normally not induce Addisonian crises in patients with anorexia nervosa. There may be a mild to moderate reduction in the urinary excretion of the neutral 17-ketosteroids and of the 11-oxygenated steroids. The eosinophilic response to ACTH is generally normal[49]. Fasting blood sugar is often reduced.

H) MISCELLANEOUS DISEASES AND CONDITIONS. The following additional diseases and conditions may superficially present some of the cardinal clinical symptomatology of Addison's disease, (except the pigmentation): Myxedema, malignant disease, severe anemias, diabetes, tuberculosis, cardiac insufficiency, chronic nephritis, chronic infections, hypoglycemia, certain blood dyscrasias, surgical hypoparathyroidism, hyperparathyroidism, hemochromatosis and nutritional deficiencies[24].

**Laboratory Aids.** Although the diagnosis of Addison's disease is still primarily made on the basis of history

and bedside clinical findings, the following laboratory studies are often useful: Plain films of the abdomen, with or without retroperitoneal pneumography and tomography, serum electrolytes, water load tests, 4-hour and 8-hour corticotropin (ACTH) response tests, plasma and urinary levels of 17-hydroxycorticoids, and glucose tolerance test[1,4,29].

**General Considerations.** 1) It is probably correct to state that at least 80% of patients suffering from chronic fatigue have an emotional origin for this symptom[13].

2) Fatigue reactions, whether due to organic pathology or psychological conflict, may be increased by fear, anxiety or anticipation, and inhibited or masked by confidence in or reassurance by the trusted physician[6].

3) Generally speaking, by the time an organic condition reaches a stage sufficient to produce fatigue, it will probably be rather readily diagnosable[24].

4) Many physicians habitually tend to ascribe the origins of fatigue to medical organic cause. The most commonly and erroneously diagnosed causes for fatigue are, in order of their frequency, 1) low blood pressure, 2) anemia, and 3) hypothyroidism. Such an explanation tends to satisfy the physician, who then proceeds with medical treatment on this basis. It is also acceptable to the patient, who may very much want an organic explanation for his symptoms. This may constitute an important reinforcement of his secondary defense (that is, the defense of the symptoms). Emotional fatigue can also be present concurrently with any physical condition[24].

5) Emotional fatigue is nearly universal in human experience[24].

6) Emotional fatigue is more socially acceptable in our society than most other symptoms of emotional origin, because society in general approves of the hard worker. Fatigue implies hard labor and overwork and is likely to secure the patient sympathy, kindly regard, and even admiration[24].

7) Boredom and monotony are often experienced or described as a feeling of fatigue, tiredness or weariness[24].

8) The complaint of generalized muscular weakness in neurasthenic reactions is partially understandable physiologically. Since the impulse for voluntary muscle activity originates in the highest cerebral centers, under volitional control, such activity is influenced by emotional factors[19].

9) The caution observed with regard to patients with Addison's disease must be extended to individuals with Simmonds' cachexia. Undue exposure to cold or heat, infections, trauma and excessive thyroid medication may precipitate these patients into adrenal insufficiency. They should not be subjected to any surgical procedure, however mild, without suitable preparations and therapy with adrenal cortical fractions. It is frequently stated that when given alone, thyroid substance may increase the metabolic demands of the patient with Simmonds' cachexia to the degree where the impaired adrenals are not able to cope with the situation[49]. However, all authorities do not agree with this[43].

10) Death in Simmonds' disease is often due to hypoglycemia. Occasionally intercurrent infections and disseminated tuberculosis occur terminally. The terminal episode is generally one of coma, associated with fever, leukocytosis and an elevation of the blood urea nitrogen.

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## SUMMARIO IN INTERLINGUA

*(See page 85 for original article)*

### Observationes de Jalnessa Inducite per Chlorpromazina, con Continuation del Uso del Agente Causative

In duo casos de jalnessa inducite per chlorpromazina le uso del agente chimic causative esseva continuate accidentalmente sin evidentia de effectos adverse. Le tableau clinic de jalnessa se resolveva e non recurreva in despecto del continuation del therapia. Iste observation subleva le question si il es necessari interrumper le therapia a chlorpromazina a causa del apparition de jalnessa. Le possibilitate de continuar le therapia a chlorpromazina in despecto del apparition de jalnessa esserea de valor therapeutic in casos selegite, specialmente in patientes neuropsychiatric. In le opinion del autores on pote sequer iste curso solmente si le patiente es hospitalisate e si le plus stricte observation clinic in le presentia de facilitates laboratorial es possibile. Le objectivo in continuar le therapia a chlorpromazina sub tal conditiones esserea le supplementation del presente studio, proque le confirmation del validitate del observationes hic reportate extenderea le utilitate de iste agente therapeutic.

Il es cognoscite que cortisona exerce duo differente effectos super le bile. Le un es hydrocholeresis o un augmento del volumine de bile; le altere es choleresis o un augmento del concentration de bilirubina e del sales biliari in le bile. Un reporto recente (Stein e Wright[11]) mentiona le disparition de jalnessa inducite per chlorpromazina post 2 dies de un therapia a cortisona. Il es interessante specular in re le possibilitate que il occurre, in patientes disveloppante jalnessa post cursos de chlorpromazina, un obstruction temporari o un insufficientia relative del activitate de cortisona al nivello hepatocellular o cholangiolitic.

Nos suggere le possibilitate que tal patientes pote continuar lor curso de chlorpromazina post le declaration de jalnessa causate per iste agente, solmente sub le conditiones de stricte observationes al hospital, proque datos additional es requirite in supporto de iste conclusiones ante que un tal practica pote esser recommendate.

PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF FEBRUARY 19, 1957

**Conversion of K-Strophanthin into a Highly Active Steroid of the Progesterone Series (19-Nor-10ξ, 14β,17α progesterone).** MAXIMILIAN EHRENSTEIN, PH.D., G. WINSTON BARBER, PH.D. (Div. of Steroid Research, Dept. of Research Medicine, University of Pennsylvania) and ROY HERTZ, M.D. (Endocrinology Branch, National Cancer Institute, Bethesda, Md.). K-Strophanthin, a readily accessible cardiac glycoside, has been converted by way of its aglycone (strophanthidin) into various 19-nor homologues of progesterone and 11-desoxycorticosterone. In particular, the following compounds were obtained in a pure crystalline form: 19-nor-11-desoxy-10 , 14β,17α-corticosterone (I), 19-nor-11-desoxy-10ξ,14β,17α-corticosterone acetate (II) and 19-nor 10ξ,14β,17α-progesterone (III). In addition, very small amounts of a by-product were isolated which possibly represents 19-nor-10ξ,14β-progesterone (IV). It is to be noted that I and III are clearly different from the corresponding 19-nor compounds having "normal" configurations which are known to be highly active as sodium-retaining and progestational agents respectively. The overall yield of III from strophanthidin is at least 2.6%.

I was found to possess no mineralocorticoid activity. In the Clauberg assay III was found to be 4 to 8 times as active as progesterone (28 rabbits). Due to the limited amounts available, IV could only be tested in a preliminary fashion. The activity appears to be at least 8 times as great as that of progesterone (8 rabbits). These findings demonstrate that in compounds of progesterone type ($\Delta^4$-3-oxo-17-methylketones) "unnatural" configurations do not necessarily preclude high progestational effectiveness. (For chemical data *cf.* G. W. BARBER and M. EHRENSTEIN, Leibigs Annalen der Chemie, 1957, in press. For biological data *cf.* M. EHRENSTEIN, G. W. BARBER and R. HERTZ, Endocrinology, 1957, in press.)

**On Fitting Equations to Experimental Data.** S. I. ASKOVITZ, M.D. (Department of Therapeutic Research, University of Pennsylvania School of Medicine). Examples of the ordinary scatter-diagram, indicating the relationship between two observed variables plotted on rectangular graph paper, are to be found in the current issues of practically all scientific journals. A common illustration in the medical literature would be a chart setting forth the change in some physiologic property following administration of different dosages of an experimental agent. There are many advantages in having an algebraic equation relating the several variables. Among these are the ability to consolidate the results of individual observation into a uniform hypothesis, to interpolate for intermediate values, to estimate beyond the range of the original data, to have an expected value with which to compare further observations, in order to estimate the accuracy of the measurements by the size of the deviations, and the like.

The decision as to which type of

equation to use: linear, parabolic, exponential, or other, may involve advanced mathematical methods. However, it often suffices to determine merely the best straight line fitting the points on the graph. The criterion of least squares is generally accepted, and the methods of computation are known to most investigators. Calculating the constants for the equation is generally a lengthy process, even for as few as three points. As a result of several problems originating in physiological laboratories, a series of simplified graphic methods have been developed over the past few years. Numerical analysis requiring a half hour or more with an electric calculating machine may be replaced by a few minutes with pencil and ruler, and with only a slight decrease in accuracy.

The basic concept behind these graphic techniques is the application of certain elementary properties of centroids to statistical procedures. The centroid is defined as the center of gravity of a combined mass. For sets of isolated points, the centroid may be located directly on the graph paper by following a few simple steps geometrically.

The essential theorem is that by assigning to each point in a series a weight equal to the x-coordinate of the point, the resulting weighted centroid will always lie upon the straight line of best fit, according to the least squares criterion. By proper selection of the coordinate axes, the determination of the best line may be accomplished by a few straightforward steps with pencil and straightedge alone, without the need for any calculations. These methods have already been applied to a variety of experimental data.

**Relation of Chemical Structure of Chlorpromazine to Its Liver Sensitizing Action.** HARRY SHAY, M.D., and HERMAN SIPLET, A.B. (Fels Research Institute and Department of Medicine of Temple University Medical Center). A report in press (Gastroenterology) indicates the sensitization reaction of the liver to the drug that appears to be the cause of chlorpromazine jaundice. One patient, who a year before had shown such a response and had recovered, again developed jaundice 12 hours after taking the first dose of a total of three tablets of chlorpromazine, 25 mg. each, during one day. After recovery from this attack, with the cooperation of the patient, it was possible to show by the administration of various substitution products of promazine and chlorpromazine, that the introduction of the chlorine atom at the two carbon position in promazine converts promazine into an antigenic compound for the liver; that replacement of the chlorine by an acetyl group removes this antigenicity; that substitution in the dimethylaminopropyl side chain attached to the nitrogen at position ten in the chlorpromazine, now also destroys the antigenicity of the chlorine containing compound for the liver; and finally the addition of the unstable oxygen atom to the sulphur in the chlorpromazine molecule in its conversion to the sulphoxide as the major excretory compound of chlorpromazine by the body (SALZMAN, N.P., *et al.*, Nature, **176**, 1122, 1955) still leaves the compound antigenic for the liver.

Using one minute and total bilirubin, serum alkaline phosphatase, glutamic oxalacetic and glutamic pyruvic transaminase as measures of an antigenic effect on the liver, we were able to show that promazine, acetyl-chlorpromazine and compazine had no antigenic effect when each was administered for a period of a week, but that the administration of only 5 mg. of chlorpromazine or a 25 mg. capsule of chlorpromazine sulfoxide was followed in a few hours by a systemic reaction and in 12 hours objective

evidence of such reaction consisting of a sharp rise in serum alkaline phosphatase and both transaminases.

**Metabolic Studies in Interstitial Calcinosis.** F. WILLIAM SUNDERMAN, JR., M.D., and F. WILLIAM SUNDERMAN, M.D., PH.D. (Division of Metabolic Research, Jefferson Medical College). Metabolic studies are reported on patients suffering from extensive interstitial calcinosis. A balance study on one of the patients demonstrated negative calcium balance on a restricted calcium diet. The patient ingested an average of 145 mg. of calcium per day and excreted 275 mg. Thirty per cent of the excreted calcium was present in the urine and 70% appeared in the feces. Since normal individuals ingesting a calcium-restricted diet characteristically develop a similar negative calcium balance, these studies support the view that interstitial calcinosis is *not* associated with disturbance in the normal response to calcium deprivation.

The administration of ammonium chloride in addition to the restricted calcium diet, increased the urinary excretion of calcium 70%. Diminution in size and number of calcium deposits following this regimen indicated that the interstitial deposits were not sequestrated but remained in reversible dynamic equilibrium.

Interstitial calcification produced experimentally in guinea pigs by a diet deficient in the anti-stiffness factor (Stigmasterol) bears resemblance to interstitial calcinosis of man. Especial note is made of the structural similarities of stigmasterol to calciferol (Vitamin $D_2$). It appears paradoxical that diets *deficient* in stigmasterol may produce interstitial calcifications, whereas a dietary *excess* of calciferol may likewise yield extraskeletal calcifications.

The pathogenesis of interstitial calcinosis appears to involve an abnormal affinity of the mucopolysaccharide of extracellular ground substance for calcium. It is noteworthy that interstitial deposits of calcium phosphate are produced without significant alterations in the concentrations of serum calcium or inorganic phosphorus, and without disturbance in the normal pattern of calcium excretion.

## SUMMARIO IN INTERLINGUA

*(See page 74 for original article)*

### Evalutation Clinic del Nove Agente Anticonvulsive, Peganon

1. Post un periodo de controlo de un anno de therapias conventional, 38 refractori e institutionalisate epilepticos chronic esseva tractate con 3-ethyl-5-phenylhydantoina (Peganon).

2. Esseva studiate casos mixte de grand e petit mal.

3. In le gruppo total, un melioration de 62 pro cento in le numero del attaccos esseva constatate. Septanta-un pro cento del casos habeva un reduction de plus que 50 pro cento in le numero del attaccos.

4. Studios hematologic routinari, tests del function hepatic, e analyses del urina esseva effectuate pro omne le patientes. Esseva notate nulle deviationes ab le valores normal e nulle signos de altere effectos toxic, per exemplo de hyperplasia gingival o de eruption cutanee. Le sol effecto lateral notate esseva un certe grado de somnolentia post multo alter doses (*i.e.*, plus que 4,5 per die).

5. Significative grados de melioration in le stabilisation del morbo esseva effectuate in iste gruppo per adder Peganon al regime jam in uso e etiam (in multe casos) per Peganon sol. Es exprimite le conclusion que le efficacia de Peganon insimul con le facto que illo es sin toxicitate face de illo un addition de alte valor al nunc disponibile drogas anticonvulsive.

# BOOK REVIEWS AND NOTICES

CLINICAL PATHOLOGY: APPLICATION AND INTERPRETATION. By BENJAMIN B. WELLS, M.D., PH.D., Director of Clinical Investigation, The Lynn Clinic, Detroit. 2nd ed. Pp. 488; 25 ills. Philadelphia: W. B. Saunders Co., 1956. Price, $8.50.

THERE is an ever increasing number of procedures being introduced into the clinical laboratory in an effort to increase the specificity and accuracy of diagnosis. As a result, the practicing physician is confronted with a choice of new tests with which he may not be familiar. It is particularly for such practitioners that the author of this volume has written a practical guide to the application and interpretation of the most essential tests currently employed in clinical pathology. The book is brief, lucidly written, contains no references, and should serve the purpose for which it is intended. C. Z.

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ETIOLOGIC FACTORS IN RENAL LITHIASIS. By ARTHUR J. BUTT, M.D., F.A.C.S., Chief, Urological Service, Baptist Hospital, Pensacola, Florida. Pp. 401; 153 ills. Springfield, Ill.: Charles C Thomas, 1956. Price, $12.50.

THE objective of the book is a better understanding of the phenomena underlying pathological states of the kidney and urine, and their relationship to calculous disease. Written by 20 experienced investigators, it is of most interest to the basic scientist, but well worth reading by the clinician.

The initial chapter on the historical background of stone formation, from the time of prehistoric man, is fascinating. The section devoted to geographic, racial, and climatic factors explodes various erroneous impressions and points out the true relationships. Colloid science in the normal and abnormal individual, with special emphasis on the effect of hyaluronidase in human urine, experimentally and clinically in stone-forming patients, is presented in detail. The Bibliography is extensive.

The obvious criticism, as in any text, is the inability to cover important material in the basic and clinical fields published after the book went to press. Thus, none of the recent work on salicylate prophylaxis is discussed.

W. F. Braasch states in the introduction, "The survey of progress made is particularly welcome, not only because it is an intelligent appraisal of advances made, but also because it can serve as a springboard for future workers in the field." L. K.

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SURGERY FOR GENERAL PRACTICE. By VICTOR RICHARDS, M.D., Professor of Surgery, Stanford University School of Medicine. Pp. 947; 476 ills. St. Louis: C. V. Mosby Company, 1956. Price, $17.50.

THIS volume is different and distinct from the usual textbook of surgery. It might properly be called an expanded handbook of surgery, although these usually dwell on minor surgery alone, while this includes the diagnostic and therapeutic aspects of many of the major surgical entities. All of the sections are concise and accompanied by excellent diagrams and photographs. Special emphasis is given to technique, particularly for those lesions most apt to be treated by the average practitioner. The section on local anesthesia is quite complete and excellent. Sections on such subjects as shock and infection discard the maze of experimental data and state the well founded facts clearly. Fractures and other traumatic lesions are given a great deal of space and attention.

This book is not recommended as the beginning text of surgery for medical students since it does not place emphasis on the principles of surgery. However, it fills a unique need for a review in surgery and as a working encyclopedia of surgery for practical application in the care of patients. R. B.

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THE IMAGE OF THE HEART. By DANIEL E. SCHNEIDER, M.D. Pp. 267; 1 ill. New York: International Universities Press, Inc., 1956. Price, $6.00.

THE author of this book presents some new concepts about the heart and the emotional and physical interaction around the heart. First he feels that the heart has its own definite sound effects which make their way into the unconscious and sometimes into the conscious. This beating, ticking, thumping, pounding, leaping, throbbing, and the like, all make the individual more "heart-conscious" than he knows. This gives the heart a prominent psychic representation in

the mind from an early age onward, which means that there is more pressure put upon the heart of the child by the parent than has ever been realized. So with psychical bombardment from within and physical stress from without a synergic (working together) action is produced with the heart the focus of it all. The heart is often symbolized in dreams by an hour-glass pattern, by a pump, an engine, a watch.

The coronary personality, the author says, has characteristics such as (a) controlled tension, (b) a physical hurry pattern, (c) a constant need for immunity from accusation, (d) a pride in a practical outlook. The author includes abnormal cholesterol, metabolism and tobacco among the factors that affect heart disease. Not easy reading but provocative for the physician interested in the mechanism of emotional stress upon an important body organ such as the heart.

O. E.

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GROUP PROCESSES. Edited by BERTRAM SCHAFFNER, M.D. Pp. 255; 23 ills. New York: Josiah Macy, Jr. Foundation, 1956. Price, $3.50.

THIS book is the second in a series publishing the results of a seminar on Group Processes sponsored by The Josiah Macy, Jr. Foundation. Frank Fremont-Smith does an admirable job as moderator. Psychology, psychiatry, psychoanalysis, the biological sciences and anthropology were represented to form an interesting and rounded discussion group.

As in the previous volume, the discussions were meaningful, lively and replete with stimulating ideas. The reviewer felt that there was somewhat less progress in the clarification of some of the concepts than in the previous volume.

William J. Sladen presented an interesting discussion of the social structure of penguins. There was a good deal of discussion of the effect of adverse climatic conditions on such behavior as mating and play. Helen Blauvelt presented a fascinating paper, "The Neomate-Mother Relationship in Goat and Man," which presented data about the importance of the very early hours of the mother newborn relationship in terms of later development. Ray L. Birdwhistell described a new technique for the analysis of group behavior in children. The concluding paper by Gregory Bateson, "This is Play" was also highly interesting. The paper dealt with metacommunication or the way in which individuals communicate the context in which their message is to be interpreted. For example, whether a gesture of aggression is to be meant as hostile or playful. Doctor Bateson presented numerous examples from animal interaction and from his work with a schizophrenic patient. He indicated that difficulties in human relationships result from misinterpretations of subtle clues in metacommunication. Much of the discussion centered around the role of play in maturation.

These two volumes on "Group Processes" are vital reading for behavioral scientists. They not only describe the most advanced concepts of outstanding thinkers in various disciplines, but also the advances which occur when these ideas are communicated and developed by interdisciplinary discussion.

A. S.

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DISEASES OF THE HEART. By CHARLES K. FRIEDBERG, M.D., Associate Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University. 2nd ed. Pp. 1161; 157 ills. Philadelphia: W. B. Saunders Company, 1956. Price, $18.00.

THIS edition remains (as the first was regarded, this Journal **219**, 468, 1950) the most comprehensive single volume text on diseases of the heart in the English language. No important advance in clinical cardiology has been overlooked. Although the double column page has been introduced, it was still necessary in order to cover the subject of clinical cardiology adequately to increase the number of pages by almost 100.

The book opens with a new section devoted to graphic methods of examination. In this section, the most serious omission in the first edition, a discussion of the range of the normal heart, is corrected.

Space allotted to valvular and congenital heart disease has been almost doubled. In these sections, the newer methods of diagnosis, the evaluation of the lesions and their amelioration or correction by surgery are for the most part adequately discussed. At times, the reviewer gains the impression that portions of the discussion are reviews of the literature uncontrolled by personal experience, an inevitable result of one person covering an entire discipline.

Discussions for medical treatment are unusually well balanced and modern. Particularly commendable is the discussion of anticoagulant treatment of myocardial infarction.

The Bibliography continues to be thorough

and includes significant references published within a few months of the appearance of this book.

The book should be on the bookshelf of everyone interested in cardiology. L. S.

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INTERESTING CASES AND PATHOLOGICAL CONSIDERATIONS AND A NUMISMATIC SUGGESTION. BY F. PARKES WEBER, M.A., M.D. F.R.C.P., F.S.A. Pp. 77; 5 ills. London: H. K. Lewis & Co., Ltd., 1956. Price, 18s. 6d.

THIS is a fascinating little book of seventy-two pages, which represents the reflections of the author, written, as he indicates, in the evening of his life. The book is a résumé of his interesting cases covering a wide range of pathological processes including vascular diseases, pulmonary affections, hamartomas and dermatological disorders, and the like. Reference is made to the "malignant carcinoid syndrome" as the Steiner Voerner syndrome. A chapter on Paracelsus with four prints of that famous individual appears near the end of this sketchy historical survey of medicine. The author concludes with a numismatic suggestion, but not being numismatically-minded, I fail to see the appeal of a "Bowl of Coins" Prize although, since we have our "Rose Bowl," etc. for our athletes, "Numismatic Bowl" would be ideal for coin collectors. This suggestion of a "Bowl of Coins" Prize coming from a physician might be misinterpreted; it might be inferred that all physicians are coin-collectors, but not in the numismatic sense.

A. P.

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DAS ERLEBNIS ALS KLINISCHE AUFGABE IN DER ÄRZTLICHEN PSYCHOTHERAPIE. BY DR. ERNST SPEER, Professor of Psychiatry, Lindau-Bodensee. Pp. 116; Munich: J. F. Lehmann, 1956. Price, DM 12.00.

A DETERMINED effort is made in this interesting but somewhat dogmatic book to reduce all psychotherapeutic measures to a procedural formula which equates improvement in the patient's adjustment with an understanding and assimilation of his life experiences. The method, based on the author's views regarding the nature of psychoneurotic phenomena, is described as "Klinik des Erlebnisses" (pathologic life experiences) and is focused on integrating the total personality in relation to its inherent and acquired capacities for experiencing life ("Erlebnisfähigkeit"). The following three types of experience are regarded as particularly important causes of emotional distress necessitating psychotherapy: a) experiences diminishing a person's self-esteem, b) disturbances in interpersonal relationships, and c) a gradual or acute loss of feelings of security.

The main value of the book lies in well-observed clinical histories as explored by an experienced and keenly interested psychiatrist. Other commendable features are the avoidance of purely philosophical ruminations in connection with the subject of human existence and the author's courageous attitude toward the body-mind dichotomy.

Less successful is the writer's attempt to hold Freud responsible for an oversimplified theory of the etiology of psychoneurosis, although his own explanation lacks depth to at least the same extent. For instance, psychopathic behavior that is described as abnormal but not psychotic is frequently referred to as a manifestation of "born degenerates in regard to whom any refined type of therapy is wasted time" (p. 65, p. 116). Another questionable statement is that an inborn tendency causes such common emotional responses as diminished self-esteem (p. 50) or lifelong feelings of insecurity (p. 96). Such formulations are much too simple to be compatible with modern genetic concepts. H. F.

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PROGRESS IN HEMATOLOGY, VOL. 1, 1956. Edited by LEANDRO M. TOCANTINS, M.D., with 27 contributors. Pp. 336; 72 ills., 1 color plate. New York: Grune & Stratton, Inc., 1956. Price, $9.75.

THIS is the first of a series of volumes whose aim will be to survey periodically the progress which is made in hematology. Advances in this field have been very rapid and it appears likely that investigations will continue at the present or even an accelerated pace in the years to come. Accordingly, this volume and its successors will undoubtedly be welcomed not only by those whose primary interest is hematology, but also by internists, pediatricians, surgeons, clinical pathologists, biochemists, and others in the clinical and basic sciences.

The current volume consists of 16 excellent reviews, all by well-known investigators. Among the interesting topics included are: Gastric Intrinsic Factor and Vitamin $B_{12}$ Interrelationships, by C. C. Ungley and R. B. Thompson; Abnormal Hemoglobins, by Wolf W. Zuelzer, James V. Neel, and Abner R. Robinson; Radioactive Phosphorus in the Treatment of Primary Polycythemia, by the late Dr. Lowell A. Erf; Hematologic Recovery

from Irradiation Injury, by Leon O. Jacobson; and Agammaglobulinemia, by David Gitlin and Charles A. Janeway.

The Editor, Dr. L. M. Tocantins, and the contributors are to be congratulated on the over-all excellence of this volume which gives the proposed series an auspicious start.

C. Z.

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CIBA FOUNDATION SYMPOSIUM JOINTLY WITH THE PHYSIOLOGICAL SOCIETY AND BRITISH PHARMACOLOGICAL SOCIETY ON HISTAMINE (April, 1955) in honor of Sir Henry Dale. Edited for the Ciba Foundation by G. E. W. WOLSTENHOLME AND C. M. O'CONNOR. Boston: Little, Brown & Company, 1956. Price, $9.00.

THE first section of this volume includes papers by the members of the two societies and reviews evidence pertaining to the occurrence of histamine in the body, its release, origin, and significance. The remainder of the book contains papers and discussions of these subjects by the society members as well as by eminent international authorities doing research on histamine and invited as guests.

Despite the numerous contributors and the complexity of the material, the subject matter is presented in extremely lucid and orderly fashion with a maximum of the essentials and a minimum of detailed experimental data. It represents in the reviewer's opinion the finest review on histamine at present available and should prove invaluable to physiologists, pharmacologists, immunologists, allergists, or any one else interested in this subject.

L. T.

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ANESTHESIA FOR OBSTETRICS. By ROBERT A. HINGSON, Professor of Anesthesia, Western Reserve University and LOUIS M. HELLMAN, Professor of Obstetrics and Gynecology, State University of New York College of Medicine. Pp. 344; 122 ills. Philadelphia: J. B. Lippincott Co., 1956. Price, $12.50.

OBSTETRIC anesthesia, like the specialty of obstetrics itself, has been accepted begrudgingly as an important phase of medical practice. Until recently deaths from hemorrhage, infection and toxemia have played such an important role in the total loss of life during pregnancy and delivery that those directly attributable to anesthesia have been overlooked. The latter have become more obvious and perhaps even more prevalent as total maternal mortality has been reduced and as more complicated and potentially dangerous methods for relieving the pain of labor and delivery have been developed by experts, and applied by untrained and unqualified physicians.

Textbooks in obstetric anesthesia have usually been written by anesthesiologists who were more concerned with the technical aspects of the administration of anesthesia than with the anesthetic requirements of the normal pregnant woman and those with various complications. "Anesthesia for Obstetrics," therefore, occupies a unique place in the field because it approaches the problem from both points of view. Hingson, a skillful anesthesiologist, has developed many of the current methods for controlling pain during childbirth and Hellman, an experienced obstetrician, has long been concerned with physiologic problems of labor and delivery. Furthermore, the authors together supervised the anesthetic management of several thousand women over a 2½-year period and are thus both familiar with the problems encountered at each end of the delivery table.

The material covered in the text includes an historical survey of obstetric anesthesia, the anatomy of the pelvis and nervous system, fetal placental relationships, the physiology and conduct of pregnancy and of normal and abnormal labor, analgesic and anesthetic methods, mortality and many other important factors. The general effects of the common drugs and anesthetic agents on both mother and infant are described and precise directions are given for their use. Incompatibilities between the available drugs also are described and tabulated. Complications such as toxemia, prematurity, bleeding, and the like, are discussed individually and suitable anesthetic techniques for each are indicated. The anesthetic causes of infant and maternal mortality are presented and methods for their prevention and treatment are described.

Hingson has long championed conduction anesthesia for delivery and naturally much more emphasis is placed on this than on the inhalation techniques but the latter are certainly adequately covered. This is particularly true of cyclopropane for the emergency administration of which Hingson has devised a "portable miniature anesthetic machine" which should be a useful addition to obstetric anesthesia. Although the authorities state that local anesthesia is by far the safest they have little enthusiasm for it and describe a method for blocking the pudendal nerve which, I am sure, they would alter if they actually used it to any extent.

The book is well illustrated with photographs and drawings many of which are in color and a number of tables augment the

material in the text. There are a few typographical errors, for instance Tables 65 and 66 are evidently reversed, but these do not detract from the value of the book and will undoubtedly be corrected in future editions. The bibliography is limited but contains key references.

This book should be studied by every physician who renders obstetric service or administers anesthesia to women during labor and delivery. J. W.

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Clinical Hematology. By Maxwell M. Wintrobe, M.D., Ph.D., Professor and Head of the Department of Medicine, University of Utah College of Medicine. 4th ed. Pp. 1184; 236 ills. and 20 plates, 18 in color. Philadelphia: Lea & Febiger, 1956. Price, $15.00.

This edition is a timely revision of what has become a standard textbook on clinical hematology. Advances in this field are being made rapidly and in many directions, so that much new material was available for incorporation in the present volume. Indeed the author added some 1600 new references, but had to delete 887 others in order to make room for the newer information. A few publications have been overlooked, and one or two appear to have been misinterpreted. This is inevitable, however, for a book of this scope. Chapters have been added on blood groups and blood transfusion, and on the abnormal hemoglobin syndromes. Also, for the first time, the terminology recommended by the "Committee for the Clarification of Nomenclature of Cells and Diseases of the Blood and Blood-Forming Organs" is included among the synonyms for the terms used by the author. This should aid individuals trained in the newer terminology in the use of this valuable textbook. C. Z.

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Psychoanalysis and Psychotherapy. By Franz Alexander, M.D., Clinical Professor of Psychiatry, University of Illinois. Pp. 299. New York: W. W. Norton & Co., 1956. Price, $4.75.

This book is the latest thinking by the author on modern psychotherapy and the role psychoanalysis has played in developing that therapy. He begins with a chapter on psychoanalysis in Western Culture followed by one on the theory of psychoanalytic treatment before launching into chapters dealing with modification in techniques in therapy. He then deals with some of the controversy aroused over a former book by himself and Dr. Thomas French entitled "Psychoanalytic Therapy." He concludes with current views about the application of psychoanalysis to the training of the physician and psychiatrist. Dr. Alexander has always been a stimulating writer and this book is no exception. It should appeal to psychiatrists and those other members of the profession who have an interest in psychotherapy requiring a knowledge of unconscious processes. O. E.

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The Dynamic Equilibrium of Body Proteins. By George H. Whipple, M.D., Professor of Pathology, Emeritus, University of Rochester. Pp. 68; 12 ills. Springfield, Ill.: Charles C Thomas, 1956. Price, $3.25.

The theme of this monograph is that there is a dynamic equilibrium of body proteins, including hemoglobin, plasma proteins, organ and tissue proteins. Reference is made to many of the basic papers which originated in the author's laboratory over the past 30 years. Students interested in protein metabolism will find this a concise presentation of the material covered in the author's more important experiments and his interpretation of the findings. C. Z.

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Clinical Recognition and Management of Disturbances of Body Fluids. By John H. Bland, M.D,. Associate Professor of Medicine, University of Vermont College of Medicine. 2nd ed. Pp. 522; 163 ills. Philadelphia: W. B. Saunders Co., 1956. Price, $11.50.

This new edition is a thorough revision of a useful and practical manual on body fluids and electrolytes. Many fundamental advances and maturing concepts have been promulgated in renal and hepatic, cardiocirculatory and hormonal influences upon the mechanics of body fluid metabolism during the four years since the initial appearance of this text. The essence of this expanding knowledge has been expertly incorporated into the discussions of the basic physiological considerations and the metabolic alterations associated with specific disease states. In addition to the classical Gamblegrams, there are frequent graphic representations of functional compartments and fluid shifts to aid the reader. The presentation of basic principles of electrolyte, hydrogen ion, and water metabolism and the application of these data to the metabolic deviations in all disease states will provide for effective management of these ubiquitous clinical problems. In his initial chapter dealing with nomenclature, the author has emphasized

the need for classification and accuracy in terminology in this field particularly with reference to the acid-base misnomers. A new section on the metabolic changes of head injury presents recent advances in this field. The chapters dealing with metabolism in surgery and trauma contain details of the current advances in these important areas. This book will be of particular value to students and physicians as a source of information concerning recent as well as standard concepts in body fluid metabolism under normal and abnormal conditions. C. S.

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THERAPY OF FUNGUS DISEASES. Edited by THOMAS H. STERNBERG, M.D., Professor of Medicine (Dermatology) and Assistant Dean for Postgraduate Medical Education, and VICTOR D. NEWCOMER, M.D., Associate Professor of Medicine (Dermatology), University of California at Los Angeles. Pp. 337; 44 ills. Boston: Little, Brown & Co., 1955. Price, $7.50.

AN international symposium on the treatment of fungus diseases was held at the University of California (Los Angeles) in June, 1955. Some 208 individuals participated, representing 24 states and 8 foreign countries. While this volume contains mostly condensations of the material presented at that symposium, the essence of each paper is satisfactorily retained. Aside from the specific information concerning the effect of various substances on the different fungal agents, there are also several interesting papers which deal with certain broad aspects of fungus problems. Included among these are: "Outstanding Problems in the Study of Antibacterial and Antifungal Antibiotics, with Special Reference to the Antibiotics of Actinomycetes," by S. A. Waksman; "Soil as the Natural Reservoir for Human Pathogenic Fungi," by L. Ajello; and "Ecology and Spread of Pathogenic Fungi," by O. A. Plunkett.

Mycologists, bacteriologists, and clinicians concerned with fungi and the clinical problems caused by them will find much valuable information in this volume. C. Z.

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HUNTERDON MEDICAL CENTER. THE STORY OF ONE APPROACH TO RURAL MEDICAL CARE. BY RAY E. TRUSSELL, M.D., M.P.H., Executive Officer, Columbia University School of Public Health and Administrative Medicine, formerly Director of the Hunterdon Medical Center. Pp. 235; 9 ills. Cambridge, Mass.: Harvard University Press, 1956. Price, $3.75.

As the subtitle, The Story of One Approach to Rural Medical Care, indicates, this is the record of the planning, building, organizing and operation of a medical center in New Jersey, about seventy miles from New York City, established to provide good medical services at a price that that semirural community could afford. "Plus and Minus," the last of its thirteen chapters, is a combined report and forecast based on somewhat less than two years of actual operation. Other chapters concern collection of funds, shaping of the plant to money available, plans of organization and administration, admission policies, relation of the hospital to other community health facilities, its development as a health center, and its unique affiliation with the New York University-Bellevue Medical Center. The book is well written, easy to read and should be of value to those interested in group practice, for the Center seems to integrate successfully extrainstitutional private practice and full-time hospital practice.

J. F.

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THE FLAVONOIDS IN BIOLOGY AND MEDICINE. A CRITICAL REVIEW. BY MAURICE E. SHILS, SC.D., AND ROBERT S. GOODHART, M.D. Pp. 101. New York: National Vitamin Foundation, Inc., 1956. Price, $2.00.

THE authors have undertaken a critical review of the literature dealing with flavonoid compounds. After surveying some 299 articles, they conclude that there is no convincing evidence for a nutritional role of these substances. Furthermore, the reviewers believe that those who claim therapeutic value for flavonoids in the treatment of vascular disorders have yet to prove their contention. This volume should be of value, therefore, to clinicians, biochemists, and nutritionists who are interested in the evaluation of flavonoids in medicine. C. Z.

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DISEASES OF THE CHEST. BY H. CORWIN HINSHAW, M.D., PH.D., Clinical Professor of Medicine, and L. HENRY GARLAND, M.B., B.CH., Clinical Professor of Radiology, Stanford University School of Medicine. Pp. 727; 634 ills. Philadelphia and London: W. B. Saunders Co., 1956. Price, $15.00.

RAPID advances in the diagnosis and treatment of many thoracic diseases tend to make textbooks out-of-date almost as soon as they are published. The student must then rely on the current literature which may be inconclusive, biased, or contradictory.

Hinshaw and Garland, each eminently qualified and experienced in his field, have collaborated on an excellent textbook. The entire field of chest disease is covered. The diagnostic approach is primarily clinical, stressing history and physical examination, as well as radiology, bronchoscopy and other ancillary procedures. Treatment recommendations are specific and sensible.

Roger H. L. Wilson has supplied an intelligible chapter on Measurement of Pulmonary Function. Foreign bodies in the air passages are discussed by Walter E. Hick. William A. Winn contributed the section on Coccidioidomycosis.

The illustrations are well chosen and adequately reproduced. Format and typography are good (with the exception of a few misprints). The bibliography is selective, up-to-date, and not overwhelming.

The book fulfills most adequately its avowed purpose—"to provide an up-to-date textbook for students and practitioners . . . sufficiently terse to permit a ready grasp of present day methods of diagnosis and treatment."

R. C.

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Annual Review of Medicine, Volume 7. Edited by David A. Rytand and William Creger, Pp. 611. Stanford, Calif.: Annual Reviews, Inc., 1956. Price, $7.00.

This is another collection of excellent reviews of important advances in selected areas of medical knowledge. The authors of the respective sections are all recognized experts in their fields. Among the topics discussed in the present volume are: "Viruses of the Upper Respiratory Tract," by G. G. Jackson; "Obstetrics," by A. C. Barnes; "The Metabolic Response to Trauma," by J. E. Rhoads, B. Roberts, and J. Helwig, Jr.; "Cardiovascular Diseases (Medical)," by B. Logue and C. Tomlin; "Immunity," by S. Raffel; and "Diseases of the Bones and Joints," by J. H. Bauer. An especially valuable list of reviews in medicine has been prepared by E. MacKay and L. MacKay.

Teachers of medicine and clinical investigators in particular, and students of medicine in general, will wish to add this volume to its predecessors in this highly valuable and recommended series. C. Z.

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A Dictionary of Dietetics. By Rhoda Ellis, Ph.D. Instructor of Foods and Nutrition, Department of Home Economics, Brooklyn College, New York. Pp. 152. New York: Philosophical Library, 1956. Price, $6.00.

This text is represented as a compilation of terms and definitions related to diet and dietotherapy. However, as a reference book for proper recognition and understanding of the language employed in the science of nutrition, it does not always provide accurate or factual material to achieve this purpose. The definitions of certain foodstuffs, food habits, and terminology applied to dietetics are, in general, well presented. Those applied to specific diseases, physiological processes and biochemical items in many instances are not entirely satisfactory. For example, on page 1, acetylation coenzyme is defined as an intermediary product formed from the products of fat digestion. Aside from the discussions and descriptions of terms referable to dietetics which are of some usefulness, there is little to recommend this volume to the medical public. C. S.

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The Year Book of Pathology and Clinical Pathology, 1955–1956 Series. Edited by William B. Wartman, B.S., M.D. Pp. 480; 161 ills. Chicago: The Year Book Publishers, Inc., 1956. Price, $6.50.

Articles abstracted for this volume were taken from journals received from January, 1955, through December, 1955. In addition, there are included three special articles: "C. P. Ceamanship" entertainingly written by J. W. Hurst; "Pulmonary Collateral Circulation: Functional Implications and Some Therapeutic Applications," by A. A. Liebow; and "The Estimation of Hemoglobin," by G. F. Stevenson.

This is a well-edited Year Book which offers a wide view of important developments in pathology and clinical pathology. Workers in other fields of medicine will also find much of interest in this volume. C. Z.

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The Inquisitive Physician. The Life and Times of George Richards Minot, A.B., M.D., D.Sc. By Francis M. Rackemann, M.D. Pp. 288; 2 ills. Cambridge: Harvard University Press, 1956. Price, $5.00.

This book gives an interesting account of the life and times of the late Dr. George R. Minot. The writer is a contemporary physician and cousin of Dr. Minot. Thus, he is well qualified to relate the more important personal and medical events of his career. Included are accounts of his years at Harvard

College and Medical School, as "House Pupil" at the Massachusetts General Hospital, his year at Baltimore, and then the period of research at the Massachusetts General and Huntington Hospitals. His development of diabetes in 1921 is described with intimate detail. This is followed by an account of Dr. Minot's work in pernicious anemia which led to the Nobel Prize in Medicine in 1934. His contributions to the success of the Thorndike Memorial Laboratory are also assessed.

Those who had the privilege of knowing and working under Dr. Minot will value this biography highly. Those who did not know him personally will find in these pages the high qualities, fine character, and inspirational leadership upon which is based the almost reverent esteem of his colleagues.

C. Z.

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THE MORPHOLOGY OF HUMAN BLOOD CELLS. By L. W. DIGGS, M.A., M.D., Professor of Medicine, University of Tennessee, DOROTHY STURM, Instructor, Memphis Academy of Arts, and ANN BELL, B.A., Instructor in Medicine, University of Tennessee. Pp. 181; 54 ills., and 31 color plates. Philadelphia: W. B. Saunders Co., 1956. Price, $12.00.

THIS atlas is written primarily as an introduction to the study of the morphology of normal and pathologic blood cells. It is, therefore, intended to be used by medical students and student medical technologists. Much can be said in praise of this work: it is beautifully illustrated, with unusual excellence and profusion of color plates; it is clearly and concisely written; and it has an adequate section on techniques and methods. Finally, the terminology employed is that which is recommended by "The Committee for the Clarification of Nomenclature of Cells and Diseases of the Blood and Blood-Forming Organs," sponsored by the American Society of Clinical Pathologists and the American Medical Association.

This book will be welcomed by students beginning the study of hematology as well as by their instructors.

C. Z.

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TUBERCULOSE UTERO-ANNEXIELLE. By JULES BRET AND ROBERT LEGROS, Gynecologue-Accoucher, Hospital of Paris. Pp. 248; 60 ills. Paris: Masson & Cie, 1956. Price, 1.600 fr.

THE diagnosis and treatment of genital tract tuberculosis have changed radically during the past few years. Although the lesions are being recognized more often than they have been in the past, pelvic tuberculosis is still a relatively uncommon lesion in most parts of the world. A comprehensive review of the subject is presented in this monograph.

In the first chapter the details of pathologic anatomy are fully described and in the second the clinical aspects of the disease are considered. The authors believe that tuberculosis is somewhat more common in congenitally deformed pelvic structures but they are not certain that such infections predispose to the development of malignancy. According to them the characteristic clinical manifestations are: an asthenic 20- to 30-year-old sterile woman whose fallopian tubes are patent but show evidence of inflammation and who also has persistent low grade fever, elevated sedimentation rate, positive tuberculin reaction and inactive endometrium.

The diagnosis is made most accurately by endometrial biopsy, but examination and culture of discharge, menstrual blood and cervical scrapings sometimes are helpful. Hysterosalpingograms may show characteristic changes; the authors advise treatment with penicillin and sulfonamides (not streptomycin) before the roentgenograms are made. The lesions, as demonstrated by Roentgen-ray, are beautifully illustrated.

Streptomycin and PAS have been used for the most part but recently they have given PAS and isoniazid. They are enthusiastic about the value of cortisone as a means of breaking down adhesions and start it 3 to 4 days after streptomycin is begun. They also use intratubal, intraperitoneal and parametrial injections of the medications. They are somewhat less enthusiastic about surgery than are some authors in this country.

The bibliography is extensive and the text is generously illustrated with reproductions of roentgenograms and photomicrographs. This book should serve as an excellent reference to the current methods for the diagnosis and treatment of pelvic tuberculosis.

J. W.

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THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY. HAND SURGERY IN WORLD WAR II. Edited by STERLING BUNNELL, M.D. Pp. 447; 224 ills. Washington: Office of the Surgeon General, Department of the Army, 1955. Price not given.

ALTHOUGH many important contributions to medicine and surgery were made by the Medical Department of the United States Army during World War II, probably none were of greater significance than those which were

made in connection with the management of injuries to the hand. Generally considered in civilian practice as minor surgery, the care of hand injuries and infections at the outbreak of World War II were relegated to outpatient departments and relatively inexperienced members of hospital staffs. The Army Medical Service recognized the major importance of the hands, their special anatomic features, and the fact that repair of hand injuries requires training in plastic, orthopedic, and neurosurgical techniques. Accordingly, there were established various overseas and continental U.S. hand centers. This volume gives an account of the work done in each of these centers. In addition there is an excellent chapter which deals with the over-all picture of the problem in the Zone of Interior. Finally, there is a splendid chapter by Dr. Bunnell entitled "Conclusions on the Care of Injured Hands in World War II Derived from the Experiences of the Civilian Consultant for Hand Surgery to the Secretary of War."

This volume is recommended to plastic surgeons, neurosurgeons, orthopedists, and general surgeons who are directly concerned with repair of injuries to hands, and to physicians in general for the basic principles of hand care which were derived from a remarkable accumulation of wartime experience. C. Z.

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## NEW BOOKS

*The Patient Speaks.* By HAROLD A. ABRAMSON, M.D., Associate Attending Physician and Chief of Allergy Clinic, Mt. Sinai Hospital, New York City. Pp. 239. New York: Vantage Press, Inc., 1956. Price, $3.50.

IN this book, the author has abstracted the results of a 4-year period of extensive psychoanalytic interviews in a single patient with allergic eczema present since infancy. Its purpose was to prove that hidden emotional factors were important, even paramount, causes of allergic eczema, not only in this patient, but by inference, in many others. The evidence furnished by the author is far from convincing. The possible influence of allergic sensitivities, notably to pollen and environmental allergens, either is disregarded or submerged by emphasis of the emotional side. Thus, the relief afforded by hospitalization or going to camp was attributed to relief from psychic stresses or to psychotherapy rather than to escape from environmental allergens; whereas, the aggravation in late August prior to going home from camp is explained upon anticipated parental contact and not upon the more likely cause, namely, the influence of pollen inhalation. While the detailed account of the patient's interviews might be interesting to psychoanalysts, it is extremely dull reading for anyone else and in the end adds nothing to the solution of the problem of the relationship of emotional factors to allergic eczema. L. T.

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*Röntgenkunde und Klinik vertebragener Krankheiten. Band 1. Die Wirbelsäule in Forschung und Praxis.* By PROF. DR. MED. HERBERT JUNGHANNS. Pp. 132; 62 ills. Stuttgart: Hippokrates Verlag, 1956. Price, DM 24.50.

THIS book represents a collection by Dr. Junghanns of papers that deal with the clinic, radiographic examination and therapy of diseases of the spine.

First, there are two papers of Dr. Gutzeit which concern the history, clinical diagnosis and medical therapy of disease of the spine.

In the next paper, Dr. Kuhlendahl reports on his results with surgical treatment of this condition. His statistics show the results in 600 patients. In 82% of them he received good or satisfactory results. In only 19 cases the results were unsatisfactory.

In the following papers special techniques of radiographic examinations are discussed by Drs. Erdmann, Fischedick, Gutmann, Cramer, Raspe, Rausch and Schluter. As these papers are very detailed, a short summary cannot be given. Reading of the original text is recommended.

W. B.

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*Women of Forty.* By M. E. LANDAU, M.D., F.R.C.S. Pp. 49. New York: Philosophical Library, Inc., 1956. Price, $2.50.

TO most women the fortieth birthday and the cessation of menstruation which follows in a few years represent emotional hurdles which are difficult to surmount. Doctor Landau, who is a mother and a gynecologist as well as the author of "Women of Forty," makes the menopause and the subsequent involutional period not only less fearsome but actually inviting. She describes the climacteric period, its symptoms and their treatment, sex life after the menopause and employment of older women in nine short, well written chapters. The entire tone is reassuring but she does not avoid important subjects such as irregular bleeding as an evidence of cancer and mental and emotional disturbances which all women fear but will not voluntarily mention. This is an excellent book with which to supplement one's own description of the menopause. It could be recommended to almost everyone, even those who are most disturbed, because its sensible approach to the problem should be of great help in allaying their fears.

J. W.

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*Neurochirurgie Fonctionnelle.* By PIERRE WERTHEIMER, Professor in the Faculty of Medicine, Lyon, France. Pp. 186; 46 ills. Paris, France: Masson et Cie, 1956. Price, 1500 francs.

THIS paperback monograph presents the observations over many years of a distinguished French neurosurgeon on various physiologic-

neurosurgical techniques for the treatment of hyperkinetic disorders, such as tremors and rigidity, epilepsy, intractable pain and psychosis. A chapter is devoted to each condition. The author has carefully presented a chronological and historical description of the development of each surgical technique. The illustrations are clear and helpful. Two chapters, one on the vascular pathology of the brain and the other on the etiology and treatment of intracranial pressure complete the monograph.

The book is written in French and will be of interest to those who wish a most recent summary and unbiased evaluation of progress in the newer neurosurgical techniques. M. S.

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*Psychiatric Education and Progress.* By JOHN C. WHITEHORN, M.D., Professor of Psychiatry, The Johns Hopkins University. Pp. 45. Springfield, Ill.: Charles C Thomas, 1957. Price, $1.75.

THIS is the publication of the two Salmon Lectures for 1955. In these lectures the discussion is confined largely to the psychotherapeutic efforts in the field. He discusses the contributions of both Freud and Meyer, not being too satisfied with either. To illustrate his own point of view, he quotes from the report of the 1952 Conference on Psychiatric Education as follows: "Human behavior is motivated and, in some psychological sense, purposeful, and rational psychotherapy is based on the assumption that the motivation of behavior can be discerned and understood, to an extent and in a manner which may enable the therapist on appropriate occasions to induce modifications of motivation or of reaction patterns by providing significant psychological experiences."

The author pleads for more concise formulations of what goes on in psychotherapy over and above "doctrinaire biases." He also pleads for the student to have an opportunity to look over the shoulder of various skilled clinicians to absorb what the author calls the "unexpressed supplement" of treatment technique. This is a thought-provoking book for the psychiatrist and teacher. O. E.

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*Mental Illness: A Guide for the Family.* By EDITH M. STERN. Revised edition. Pp. 95. New York: Harper & Brothers, 1957. Price, $2.50.

THIS is a third revision of a valuable and successful book that generously fulfills the claims of its title. It discusses such things as meeting mental illness when it appears, deciding upon public or private hospitalization, taking the patient to the hospital, letters and visits. A discussion of life in the hospital as well as discharge, recovery and home care is also included. There is a foreword by Dr. William C. Menninger. This book can be recommended both for the physician's library and for patient consumption. O. E.

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*La Fatigue.* By DR. PAUL CHAUCHARD. Pp. 128; 4 ills. Paris: Presses Universitaires de France, 1956. Price, not given.

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*Advisory Group on Veterinary Public Health. Report.* World Health Organization Technical Report Series No. 111. Pp. 26. Geneva: World Health Organization, 1956. Price, $.30.

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*Chronicle of the World Health Organization,* **10,** No. 8, *August, 1956.* Pp. 40; 6 ills. Geneva: World Health Organization, 1956. Price, $.30.

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*Chronicle of the World Health Organization,* **10,** *No. 11, November, 1956.* Pp. 48; 2 ills. Geneva: World Health Organization, 1956. Price, $.30.

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*Chronicle of the World Health Organization,* **10,** *No. 12, December, 1956.* Pp. 33; 5 ills. Geneva: World Health Organization, 1956. Price, $.30.

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*Syphilis-Metasyphilis.* By DR. MED. ARMIN MÜLLER. Pp. 170; 6 ills. Stuttgart: Hippokrates-Verlag, 1955. Price, DM 13.80.

THIS is a speculative venture in biologic philosophy in which the author examines the adaptation of the *Treponema pallidum* to its role of venereal pathogen in man; and the teleological significance of the metasyphilitic manifestations in their destructive attack on the viscera. Although the argument at times becomes somewhat tenuous and fine-spun, the author never loses the interest and rarely the approval of the reader. Physicians with an interest in the broader aspects of human disease in relation to basic biological concepts will find this an interesting and challenging work, although it requires a thorough knowledge of German.

R. K.

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*Practical Medical Mycology.* American Lecture Series No. 248. By EDMUND L. KEENEY, A.B., M.D. Pp. 145; 12 ills. Springfield, Ill.: Charles C Thomas, 1955. Price, $3.75 and $4.50.

THIS text presents the salient features of the various human diseases that are produced by fungi. Each chapter includes a brief historical sketch of the particular condition, pathological and diagnostic features of the disease, the accepted treatment and a list of significant references. In most instances there is a line drawing that presents these data for easier remembering. The author is to be complimented upon this simple and practical presentation of an important topic. The book is highly recommended.

R. K.

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*Veterans Administration Technical Bulletins, Series 10, Volume VII, 1954.* Pp. 194. Washington: Veterans Administration, 1955.

THIS is the seventh volume of a series of technical bulletins issued by the Veterans Administration, presumably under the able editorship of Dr. Arthur H. Walker, although his name does not appear in this volume. These bulletins, eleven in number, bring to the Medical Officers of the Veterans Administration some very timely, authoritative and concise statements of clinical problems. It is unfortunate that these volumes are not for sale, since they would find a wide appeal. However, medical libraries can obtain them upon request and should make use of this privilege. R. K.

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*Allergy and Anaphylaxis.* By KEIZO NAKAMURA, Professor of the Nippon Medical School, Tokyo. Pp. 114; 35 ills. Tokyo: Keizo Nakamura, 1954.

THE author presents the basic principles of anaphylaxis as they have been developed over the years and attempts to apply them to certain aspects of human hypersensitiveness. There follow some experimental observations by the author and his associates on the basic nature of allergic phenomena. The book is of interest to those working in immunological research.
R. K.

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*Joint FAO/WHO Conference on Food Additives. Report.* World Health Organization Technical Report Series, No. 107. Pp. 14. Geneva: World Health Organization, 1956. Price, $.30.

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*Expert Committee on Biological Standardization. Ninth Report.* World Health Organization Technical Report Series, No. 108. Pp. 20. Geneva: World Health Organization, 1956. Price, $.30.

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*Venereal Diseases. A Survey of Existing Legislation.* Pp. 44. Geneva: World Health Organization, 1956. Price, $.70.

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*Some Protozoan Diseases of Man and Animals: Anaplasmosis, Babesiosis, and Toxoplasmosis.* By CLARENCE R. COLE AND 19 OTHER AUTHORS. Annals New York Academy of Sciences, **64**, Art. 2, pp. 25–277. New York: New York Academy of Sciences, 1956. Price, $3.50.

A SERIES of 9 papers on two human diseases, anaplasmosis and toxoplasmosis, and 4 papers on babesiosis, a protozoan blood disease of animals, presented before a Conference held before the Section of Biology of the New York Academy of Sciences. They discuss the manifestations, diagnosis, transmission, treatment and control.

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*Effects of Natural Selection on Human Genotypes.* By L. D. DUNN, HOWARD LEVENE AND R. B. MCCONNELL, Annals New York Academy of Sciences, **63**, Art. 1, pp. 1–32. New York: New York Academy of Sciences, 1956. Price, $1.25.

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*Fertilization.* By LORD ROTHSCHILD, G.M., Sc.D., F.R.S. Pp. 170; 34 ills. London: Methuen & Co., Ltd.; New York: John Wiley & Sons, Inc., 1956. Price, $3.50.

THE author confines the material presented in "Fertilization" to ". . . the life of the egg from the attaching of the fertilizing spermatozoon to the fusion or apposition of the male and female pronuclei. This process, except in mammalian eggs, usually takes a little less than one hour. . . ." He describes the mechanics of fertilization in many lower animal forms as well as in mammals and in addition briefly considers the process in certain plants.

He first describes the morphologic changes which occur in the germ cells during fertilization and then considers the chemical and metabolic processes which have been studied. In the final chapter he lists 15 specific problems which need further elucidation before many of the questions concerning the precise mechanism of fertilization can be answered.

This volume contains little to attract general interest. It is highly technical and contains little material which, in its present form at least, will be helpful to the clinician. In fact the author states definitely that the book was prepared ". . . for those who have read, or are reading Gray's 'Experimental Cytology,' Heilbrunn's 'Outline of General Physiology,' Fruton and Simonds' 'General Biochemistry,' Hober's 'Physical Chemistry of Cells and Tissues' and similar textbooks. . . ."
J. W.

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*Report of the Medical Research Council for the Year 1954–1955.* Pp. 286. London: Her Majesty's Stationery Office, 1956. Price, 10 s. net.

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*Field Trial of Typhoid Vaccines, Water Pollution in Europe, Malaria Eradication.* Chronicle of the World Health Organization, Vol. 10, No. 6, June, 1956. Pp. 35. Geneva: World Health Organization, 1956. Price, $.30.

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*Ninth World Health Assembly. Nurses: Their Education and Their Role in Health Programmes.* Chronicle of the World Health Organization, Vol. 10, No. 7, July, 1956. Pp. 41. Geneva: World Health Organization, 1956. Price, $.30.

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*The Rabbit in Experimental Physiology.* By HAROLD M. KAPLAN, Southern Illinois University. Pp. 70; 4 ills. New York: Scholar's Library, 1956. Price, $2.50.

*Men with Golden Hands (A Book of Surgical Miracles)* By E. H. G. Lutz. Translated by W. H. Johnson. Pp. 269. New York: Appleton-Century-Crofts, Inc., 1956. Price, $3.75.

This is a dramatic presentation of unusual surgical cases. Written primarily for the layman, this book consists of fifteen short essays. The connection between all stories is the idealization of the surgeon who is usually a professor in the European tradition.

This book will probably make the public more understanding of the surgeon's problems and for this reason can be recommended.

R. T.

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*Administrative Medicine:* Transactions of the Fourth Conference, October 31, November 1 and 2, 1955, Princeton, New Jersey. Edited by George S. Stevenson, M.D., National and International Consultant, National Association for Mental Health, New York, New York. Sponsored by the Josiah Macy, Jr. Foundation, New York, New York. Pp. 251; 11 ills. New York: Josiah Macy, Jr. Foundation, 1956. Price, $4.25.

As stated in the preface of this book, the Josiah Macy, Jr. Foundation has organized conference groups to discuss urgent problems in the field of medicine and health.

The book is a symposium of the views of fifteen physicians, deans, sociologists and others as members of the panel, and eight guests, all prominent or interested in administrative medicine. The theme of the discussions is the measurement of needs for medical and related services, and the evaluation and assessment of various programs such as health insurance and group practice to meet these needs. Inasmuch as discussion, questions, remarks and comment are published verbatim, a short summary with conclusions, if any, of the topic discussed would seem desirable. The book has an autobiographical sketch of participants and an Index. Should be of interest to all persons interested in administrative medicine.

D. S.

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*Staphylococcal Infections.* By David E. Rogers and 30 others. Pp. 190; illustrated. New York: New York Academy of Sciences, 1956. Price, $4.50.

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